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Use of Statins and the Development of Incident Diabetes Mellitus: A Retrospective Cohort Study

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Use of Statins and the Development of Incident Diabetes Mellitus: A Retrospective Cohort Study

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Dedication

I dedicate this treatise to my dear wife, Adebola, for her patience, love, sacrifices, endurance, encouragement, and support.

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Abstract

Use of Statins and the Development of Incident Diabetes Mellitus: A Retrospective Cohort Study

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Statins are pharmaceutical agents used in lowering blood cholesterols levels. Several landmark statin trials have demonstrated the beneficial effects of statins in both primary and secondary prevention of cardiovascular disease. Although statins are generally safe and well tolerated, several studies have suggested that statins are associated with a moderate increase in risk of new-onset diabetes. These observations prompted the FDA to revise statin labels to now include a warning of an increased risk of incident diabetes mellitus as a result of increases in glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG). However, few studies have used US-based data to investigate this statin-associated increased risk of diabetes. Thus, the purpose of this study was to evaluate whether statin use was associated with an increased risk of new-onset diabetes. In addition, this study evaluated whether diabetes risk was increased when patients received intensive statin doses.

This study was a retrospective cohort analysis that utilized data from the *Thomson Reuters MarketScan® Commercial Claims Database* for the period of 2003 – 2004. The study population included new statin users who were aged 20 – 63 years at index and who do not have a history of diabetes.

Among the study population (N=116,224), 6.5% (or N=7,593) had incident diabetes. Compared to no statin use, statin use was significantly associated with increased risk of incident diabetes (HR=2.752; 99% C.I.=2.535 – 2.987; $p<0.0001$). In addition, each statin type (i.e., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) was associated with about a two-fold increase in risk of diabetes. Diabetes risk was highest among lovastatin users and lowest among rosuvastatin users. Furthermore, diabetes risk was higher among intensive-dose statin users compared to moderate-dose statin users (HR=1.540; 99% C.I.=1.393 – 1.704; $p<0.0001$).

Because of the proven benefits of statins in both primary and secondary prevention of cardiovascular disease, and because the potential for diabetogenicity differs among statins, health care professionals should individualize statin therapy by identifying patients who would benefit from less diabetogenic statin types. This could help optimize treatment by providing the highest benefit achievable while reducing the number of patients developing diabetes under statin therapy.

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CHAPTER 1: INTRODUCTION

In February 2012, the US Food and Drug Administration (FDA) approved important safety labeling changes for pharmaceuticals commonly called statins. Statins are pharmaceutical agents used to lower blood cholesterol level. The labeling change for statins now includes an increased risk of incident diabetes mellitus as a result of increases in glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG) that was found to be associated with statin therapy.[1] The FDA based its decision on a combination of results from randomized controlled trials (RCTs),[2] meta-analyses of RCTs,[3] systematic review,[4] and a few observational studies,[5] which indicated an increased risk of incident diabetes due to statin therapy. Other published results from primary and secondary statin

[1] Food and Drug Administration. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. 2012; Available at: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Accessed 5/12, 2012.

[2] Thongtang N, Ai M, Otokozawa S, et al. Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation. Am J Cardiol. 2011;107(3):387-92; Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, and Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. J Am Coll Cardiol. 2010;55(12):1209-16; Sabatine MS, Wiviott SD, Morrow DA, McCabe CH, and Cannon CP. High-dose atorvastatin associated with worse glycemic control: a PROVE-IT TIMI 22 substudy. Circ J. 2004;110(Suppl I):S834; Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207.

[3] Mills EJ, Wu P, Chong G, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM. 2011;104(2):109-24; Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735-42; Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, and Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care. 2009;32(10):1924-9.

[4] Kostapanos MS, Liamis GL, Milionis HJ, and Elisaf MS. Do statins beneficially or adversely affect glucose homeostasis? Curr Vasc Pharmacol. 2010;8(5):612-31.

[5] Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med. 2012;172(2):144-52; Sukhija R, Prayaga S, Marashdeh M, et al. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Investig Med. 2009;57(3):495-9.

prevention trials,[6] meta-analyses of RCTs,[7] and observational studies[8] not cited by the FDA also furthered the discussion of the association between statin use and the risk of

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[6] Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007; Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. Ibid.1998;279(20):1615-22; Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155-63; Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Ibid.2003;361(9364):1149-58; Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Ibid.2002;360(9346):1623-30; Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-7; Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9; Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339(19):1349-57; Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Ital Heart J. 2000;1(12):810-20; MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22; Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357(22):2248-61; Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9645):1231-9; Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation. 2001;103(3):357-62.

[7] Baker WL, Talati R, White CM, and Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2010;87(1):98-107; Coleman CI, Reinhart K, Kluger J, and White CM. The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2008;24(5):1359-62; Naci H, Brugts J, and Ades T. Comparative tolerability and harms of individual statins: A study-level network meta-analysis of 246 955 participants from 135 randomized controlled trials. Circ Cardiovasc Qual Outcomes. 2013; Navarese EP, Swiatkiewicz I, Sukiennik A, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol. 2013;111(8):1123; Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305(24):2556-64.

[8] Chen CW, Chen TC, Huang KY, Chou P, Chen PF, and Lee CC. Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country. PLoS One. 2013;8(8):e71817; Jick SS, and Bradbury BD. Statins and newly diagnosed diabetes. Br J Clin Pharmacol. 2004;58(3):303-9; Izzo R, de Simone G, Trimarco V, et al. Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk. Nutr Metab Cardiovasc

incident diabetes. Several studies have also discussed whether the cardiovascular gain by using high dose statins was offset by an increased risk in diabetes.[9]

The potential increased risk in diabetes associated with statin use is significant because dyslipidemic patients being treated with statins already have a baseline increased risk of diabetes due to abnormal lipid levels, combined with comorbidities such as high blood pressure, increased weight and body mass index (BMI), metabolic syndrome, and cardiovascular diseases.

Increased risk of diabetes as a result of statin use is not a desirable outcome because of the already increasing incidence and prevalence of prediabetes and diagnosed

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Dis. 2013;23(11):1101-6; Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, and Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ. 2013;346:f2610; Danaei G, García Rodríguez LA, Fernandez Cantero O, and Hernán MA. Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival. Diabetes Care. 2013;36(5):1236; Ko DT, Wijeysundera HC, Jackevicius CA, Yousef A, Wang J, and Tu JV. Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins. Circ Cardiovasc Qual Outcomes. 2013;6(3):315-22; Ma T, Chang MH, Tien L, Liou YS, and Jong GP. The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study. Drugs Aging. 2012;29(1):45-51; Ma T, Tien L, Fang C-L, Liou Y-S, and Jong G-P. Statins and new-onset diabetes: a retrospective longitudinal cohort study. Clin Ther. 2012;34(9):1977-83; Wang KL, Liu CJ, Chao TF, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol. 2012;60(14):1231-8; Zaharan NL, Williams D, and Bennett K. Statins and risk of treated incident diabetes in a primary care population. Br J Clin Pharmacol. 2013;75(4):1118-24.

[9] Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495-504; LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. Ibid.2005;352(14):1425-35; Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010;376(9753):1658-69; Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Ibid.:1670-81; de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292(11):1307-16; ibid.; Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. Ibid.2005;294(19):2437-45; ibid.; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."; Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

diabetes which is significantly contributing to increasing rates of morbidity and mortality among Americans.[10] Diabetes is the seventh leading cause of death in the United States with attendant complications such as kidney failure, heart attacks, strokes, and amputations.[11] Diabetes also imposes a substantial economic burden on the US population in the form of increased direct and indirect medical costs.[12]

Several RCTs have examined the association between statins and incident diabetes. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was one of the RCTs the FDA used in reaching a decision to change the labeling for all statins.[13] Coincidentally, the results from this study also was thought to be influential in the decision by the FDA to expand the labeling of statins for use in primary prevention because the rosuvastatin group had a significant 44% reduction in major coronary events compared to placebo group.[14] Moreover, a somewhat downplayed secondary outcome of the study results also showed that rosuvastatin was significantly associated with a 26% increased risk of diabetes.[15]

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[10] Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

[11] Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.

[12] American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013;36(4):1033-46.

[13] Ridker PM et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein."

[14] Kaul S, Morrissey RP, and Diamond GA. By jove! What is a clinician to make of JUPITER? Arch Intern Med. 2010;170(12):1073-77.

[15] Ridker PM et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein."; ibid.

Similar to the JUPITER study, the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study found a 32% increased risk of diabetes associated with pravastatin use.[16] The results from the JUPITER and PROSPER studies were consistent with results from other RCTs which showed statins to be associated with increased risk of diabetes. While some of these associations were statistically significant,[17] a majority were not statistically significant.[18] The preponderance of non-significant results may be due to the fact that the RCTs were not primarily designed to measure statin-induced diabetes but were designed to examine the benefit of cardiovascular protection provided by statins. Moreover, results from other RCTs showed that statins may be associated with a reduced risk (or protective effect) of diabetes rather

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[16] Shepherd J et al., "Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial."

[17] Koh KK et al., "Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients."; Sabatine MS et al., "High-dose atorvastatin associated with worse glycemic control: a PROVE-IT TIMI 22 substudy."; Thongtang N et al., "Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation."

[18] "Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)."; Nakamura H et al., "Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial."; Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Ibid.2003;361(9364):1149-58; Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Ibid.1994;344(8934):1383-9; "MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial."; Kjekshus J et al., "Rosuvastatin in older patients with systolic heart failure."; Tavazzi L et al., "Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial."

than being associated with an increased risk.[19] A majority of these statin protective effects were, however, not statistically significant.[20]

Evidence from meta-analyses of RCTs cited by the FDA,[21] and other meta-analyses of RCTs[22] supports the hypothesis that statins may be associated with a moderate increase in risk of diabetes. Statin therapy was significantly associated with a 9% increased risk of incident diabetes in the 2010 meta-analysis of 19 RCTs by Sattar et

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[19] Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."; Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."; "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."; "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)."; Freeman DJ et al., "Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study."

[20] Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."; Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."; "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."; "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)."

[21] Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."; Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."; Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."

[22] Baker WL et al., "Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis."; Coleman CI et al., "The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials."; Naci H et al., "Comparative tolerability and harms of individual statins: A study-level network meta-analysis of 246 955 participants from 135 randomized controlled trials."; Navarese EP et al., "Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus."; Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

al.,[23] the 2011 meta-analysis of 17 RCTs by Mills et al.,[24] and the 2013 meta-analysis of 55 RCTs by Naci et al.[25] Meanwhile, the 2009 meta-analysis of 5 RCTs by Rajpathak et al. reported the highest significant increased risk of incident diabetes of 13 percent.[26]

Evidence from observational studies appears to follow that observed from RCTs and meta-analyses of RCTs with respect to the direction and strength of association between statin therapy and incident diabetes. The 2012 prospective cohort study by Culver et al. showed that statin use was associated with a 47% increased risk of new-onset diabetes mellitus among postmenopausal women participating in the longitudinal Women's Health Initiative (WHI) study.[27] A 2009 retrospective cohort study that examined the effect of statins on fasting plasma glucose in diabetic and nondiabetic patient population reported that statin use was significantly associated with a rise in FPG in both patient groups.[28] Two retrospective cohort studies published in 2012 by Wang et al.[29] and Zaharan et al.[30] reported a 15% and 20% increased risk in diabetes, respectively. A more recent retrospective cohort study authored by Danaei et al.[31] in 2013, reported

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[23] Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."
[24] Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."
[25] Naci H et al., "Comparative tolerability and harms of individual statins: A study-level network meta-analysis of 246 955 participants from 135 randomized controlled trials."
[26] Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."
[27] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."
[28] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
[29] Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."
[30] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."
[31] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."

that a 14% increased risk of diabetes was associated with statin users compared to non-users of statins.

In general, evidence points to a moderate increase in the risk of diabetes mellitus that is associated with statin use in observational studies. While a majority of the studies indicates a significant increase in the risk of incident diabetes that is associated with statin use,[32] fewer studies indicate a non-significant increase in risk,[33] or a protective effect of certain types of statins against diabetes.[34]

In general, evidence from RCTs, meta-analyses of RCTs, and those from observational studies tend to suggest that statin therapy is associated with a moderate increase in risk of incident diabetes mellitus.

The main purpose of the present study is to examine whether the use of statins increases the risk of incident diabetes mellitus. This is warranted because current evidence linking statin therapy to the development of incident diabetes has been inconsistent. While some studies indicate a moderate, statistically significant increase in

[32] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

[33] Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."; Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

[34] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

risk of diabetes with statin therapy,[35] some indicate that statins reduce the risk of diabetes,[36] while others suggest that the increase in risk is not statistically significant.[37]

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[35] Koh KK et al., "Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients."; Sabatine MS et al., "High-dose atorvastatin associated with worse glycemic control: a PROVE-IT TIMI 22 substudy."; Thongtang N et al., "Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation."; Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."; Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."; Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."; Baker WL et al., "Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis."; Coleman CI et al., "The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials."; Naci H et al., "Comparative tolerability and harms of individual statins: A study-level network meta-analysis of 246 955 participants from 135 randomized controlled trials."; Navarese EP et al., "Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus."; Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

[36] Freeman DJ et al., "Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study."; Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."; ibid.; Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."; "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."; "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."; Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."

[37] "Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)."; Nakamura H et al., "Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial."; Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Ibid.2003;361(9364):1149-58; Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Ibid.1994;344(8934):1383-9; "MRC/BHF Heart Protection Study of

In addition, a majority of the observational studies examining the association between statin use and the development of diabetes were conducted using non-US population data. Currently, 12 observational studies have examined the association between statins and incident diabetes. Only two of these studies used population data that originated from the US.[38] The other published studies were from Taiwan (4 studies),[39] Canada (2 studies),[40] the United Kingdom (2 studies),[41] Ireland (1 study),[42] and Italy (1 study).[43] Thus, there is a need to further examine this topic among the US population. This is because the US population may be different from other populations in terms of the prevalence of risk factors such as overweight, obesity, and cardiovascular diseases that

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cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial."; Kjekshus J et al., "Rosuvastatin in older patients with systolic heart failure."; Tavazzi L et al., "Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."; Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

[38] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

[39] Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."

[40] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."

[41] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

[42] Zaharan NL, Williams D, and Bennett K. Statins and risk of treated incident diabetes in a primary care population. Ibid.2013;75(4):1118-24.

[43] Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

may put people at an increased risk of diabetes, independent of the effects of statins.[44] For example, the US has the highest rate of obesity (defined as BMI of 30 or greater – an independent risk factor for diabetes and cardiovascular disease) among all high income population such as those found in Canada and Europe.[45] This is in contrast to people from East Asia (e.g., Taiwan, China, Japan, etc.) who are known to have mean BMIs that are among the lowest in the world.[46]

Furthermore, this study is needed because a majority of the previous observational studies that examined the association between statin therapy and new diabetes did not control for important variables such as BMI or obesity,[47] statin dosages,[48] and

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[44] Graham I, Cooney MT, Bradley D, Dudina A, and Reiner Z. Dyslipidemias in the prevention of cardiovascular disease: risks and causality. Curr Cardiol Rep. 2012;14(6):709-20; Kirkman MS, Odegard PS, Pratley RE, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650; Lawrence JM, Contreras R, Chen W, and Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. Diabetes Care. 2008;31(5):899-904.

[45] Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011;377(9765):557-67.

[46] Ibid.

[47] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."

[48] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

hyperlipidemia or low-density cholesterol level.[49] These uncontrolled variables may confound the association between statin therapy and development of new diabetes.

The inconsistent findings, few US-based studies, and the weak association linking statin therapy to the development of diabetes as shown by previous studies call for further investigation using a rigorous methodological and analytical approach. Therefore, the purpose of this study is to determine whether the use of statins increases the risk of diabetes mellitus using a US database. Thus, this study will compare the incidence of diabetes mellitus between statin users and non-statin users using a retrospective cohort design.

[49] Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."; Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."

CHAPTER 2: LITERATURE REVIEW

2.1 SECTION I: HYPERLIPIDEMIA AND CARDIOVASCULAR DISEASE

2.1.1 Introduction

Hyperlipidemia, hyperlipemia or hyperlipoproteinemia are terms used to describe lipid metabolism disorder where blood levels of artherogenic lipoproteins (most especially, LDL-C) are elevated, and where there could be associated decreased levels of protective lipoproteins (e.g., high density lipoprotein cholesterol, HDL-C). These terminologies may be confused with dyslipidemia, which refers to abnormal plasma lipoprotein level that can be either increased (hyperlipidemia) or decreased (hypolipidemia).[50] However, for this study, hyperlipidemia and dyslipidemia may be used interchangeably.

2.1.2 Etiology of Dyslipidemias

Most dyslipidemias are hyperlipidemias, and can result from either primary (genetic) or secondary disorders of lipid metabolism.[51] Primary dyslipidemia can be monogenic (single gene defect) or polygenic (multiple genes) in origin, and include disorders such as familial lipoprotein deficiency, apoprotein CII deficiency, familial hypercholesterolemia, familial apo B-100 deficiency, type III familial, polygenic hypercholesterolemia, familial combined hyperlipemia, and familial

[50] Eaton CB. Hyperlipidemia. Primary care. 2005;32(4):1027-55.
[51] Angelico F, Baratta F, and Del Ben M. Current ways of treating dyslipidemias to prevent atherosclerosis. Ther Apher Dial. 2013;17(2):125-9.

hypertriglyceridemia.[52] Secondary dyslipidemia often results from such causes as diabetes mellitus, metabolic syndrome, cholestasis, hypothyroidism, nephrotic syndrome, impaired renal function, alcoholism and drug-induced (e.g., use of diuretics, beta blockers, and estrogens).[53]

2.1.3 Lipoprotein Classification

Cholesterols are fat-like substances in the blood that contain both lipids and proteins, thus the term 'lipoprotein.'[54] Lipoproteins are important for cellular metabolism. They serve as a transportation vehicle for free fatty acids and plasma cholesterol. They are also responsible for several important biological functions that include energy for cells and tissues, production of steroid hormone, and bile acid formation. However, abnormal lipoprotein metabolism is implicated in the development of atherosclerosis and coronary heart disease (CHD), with over 70% of people with CHD also having lipid disorders.[55]

There are five major lipoprotein particles involved with disorders of lipid metabolism. These include chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-

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[52] Ibid.
[53] Ibid.
[54] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
[55] Eaton CB, "Hyperlipidemia."

density lipoprotein (HDL) cholesterols. Others important lipoproteins include chylomicron remnants (partially degraded chylomicrons) and lipoprotein(a).[56]

Chylomicrons

Among the lipoprotein particles, chylomicrons have the highest density (>0.95g/mL). Chylomicrons transport large amounts of triglycerides (TG). People with TG>500mg/dL have elevated amount of the lipoprotein.[57]

VLDL

These are TG-rich lipoproteins with a density of 0.95 – 1.006g/mL. They make up 10-15% of the total serum cholesterol. People with TG of 150 – 500mg/dL have elevated levels of the lipoprotein.[58]

IDL

Intermediate density lipoproteins have a density of 1.006 – 1.019g/mL. They transport both TG and cholesterol esters. People with total cholesterol (TC) or TG of around 300mg/dL have elevated levels of the lipoprotein.[59]

LDL

Low density lipoproteins (informally called the bad cholesterol) have a density of 1.019 – 1.063g/mL, and make up 60 – 70% of the total serum cholesterol in the body. They transport large amounts of cholesterol esters but smaller amounts of TG. LDL is the

[56] Ibid.
[57] Ibid.
[58] Ibid.
[59] Ibid.

main lipoprotein implicated in atherosclerotic cardiovascular disease (ASCVD). Levels should be less than 100mg/dL in people at high risk of CHD.[60]

HDL

High density lipoproteins (informally called the good cholesterol) have the highest density of between 1.063 and 1.21g/mL, and make up about 20 – 30% of the total body serum cholesterol. They help remove excess cholesterol from the body and transport it to the liver for excretion, hence their anti-atherogenic properties. Levels > 60mg/dL are believed to be optimal for cardiovascular protection.[61]

2.1.4 Epidemiology of Hyperlipidemia

High levels of LDL-C (defined as level that is at or above LDL-C goal for a patient's cardiovascular risk group, or current use of cholesterol medication) is a major risk factor for cardiovascular diseases. Even though Americans have made significant progress with regard to controlling their blood levels of total cholesterol over the past decade and a half,[62] the percentage of Americans with high levels of LDL-C still remains high. According to data from the 2005 – 2008 National Health and Nutrition Examination Survey (NHANES), 71 million (34%) American adults aged 20 years and older had high

[60] Ibid.
[61] Ibid.
[62] Carroll MD, Kit BK, and Lacher DA. Total and high-density lipoprotein cholesterol in adults, 2009–2010. Hyattsville, MD: Centers for Disease Control and Prevention's National Center for Health Statistics, Division of Health and Nutrition Examination Surveys; 2012.

LDL-C, but only 34 million (48.1%) were treated, and 23 million (33.2%) had their LDL-C controlled.[63]

The prevalence of high LDL-C among Americans differs by age, gender, race/ethnicity, and insurance status.[64] The prevalence of high LDL-C is highest among those aged 65 years or older (58.2%) compared to those aged 40-64 years (41.2%) and 20 – 39 years (11.7%). The percentage of males (36.2%) who had high LDL-C is higher than that for females (31.0%). Among race/ethnic populations, non-Hispanic whites (34.5%) have the highest prevalence of high LDL-C compared to non-Hispanic blacks (30.4%) and Mexican-Americans (27.7%). With regard to insurance status among Americans, the prevalence of high LDL-C is highest among those with Medicare (58.9%) compared to those with public insurance (38.6%), private insurance (27.8%), and the uninsured (25.0%).[65]

2.1.5 Epidemiology and Economic Burden of Cardiovascular Disease

Data show that about half of Americans (49%) have at least one of the three major risk factors (i.e., high LDL-C, high blood pressure, and smoking) responsible for the high burden of cardiovascular disease among Americans.[66] Cardiovascular disease (CVD) is the leading cause of death among the various race/ethnic groups in the United States,

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[63] Centers for Disease Control and Prevention. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008. MMWR. 2011;60(4):109-14.
[64] Ibid.
[65] Ibid.
[66] Centers for Disease Control and Prevention. Million Hearts: strategies to reduce the prevalence of leading cardiovascular disease risk factors in United States. MMWR. 2011;60(36):1248-51.

accounting for 600,000 deaths annually (i.e., 1 in every 4 deaths).[67] The proportion of all deaths attributed to heart disease is highest among whites (25.1%) compared to African Americans (24.5%), Asians or Pacific Islanders (23.2%), Hispanics (20.8%), and American Indians or Alaska Natives (18.0%).[68]

Currently, 11.3% (26.6 million) of non-institutionalized American adults have diagnosed heart disease.[69] This number is projected to increase to 40.5% (116 million) by 2030.[70] CHD (the most common form of CVD) is also the leading cause of death worldwide, with an average American having a coronary event (e.g., angina pectoris, acute coronary syndrome, silent myocardial ischemia, and sudden cardiac death) approximately every 25 seconds, and another dying of these events approximately every 60 seconds.[71]

CVD is responsible for 17% of the overall national health expenditures.[72] This cost is projected to increase substantially over the next two decades. The total direct medical costs of CVD are projected to triple, from $273 billion in 2010 to $818 billion in

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[67] Murphy SL, Xu JQ, and Kochanek KD. Deaths: Final data for 2010. Natl Vital Stat Rep. 2013;61(4).
[68] Heron M. Deaths: leading causes for 2008. Ibid.2012;60(6):1-94.
[69] Blackwell DL, Lucas JW, and Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. National Center for Health Statistics. Vital Health Stat. 2014;10(260).
[70] Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123(8):933-44.
[71] Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Ibid.2012;125(1):e2-e220.
[72] Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Ibid.2011;123(8):933-44.

2030, while the indirect costs due to lost productivity are estimated to increase by 61% from $172 billion in 2010 to $276 billion in 2030.[73]

2.1.6 Dyslipidemia and the Risk of Atherosclerotic Cardiovascular Disease

Several risk factors – both lipid and non-lipid – are implicated in the development of ASCVD. Lipid risk factors include high levels of LDL-C and TG, and low levels of HDL-C. Modifiable non-lipid risk factors include hypertension, cigarette smoking, diabetes, metabolic syndrome, overweight and obesity, physical inactivity, and atherogenic diets. Non-modifiable, non-lipid risk factors include older age, male sex, and family history of premature CHD.[74] Other currently emerging risk factors considered important in the development of ASCVD include lipoprotein remnants, lipoprotein (a), small LDL particles, HDL subspecies, apolipoprotein B (apo B), apolipoprotein A-I, TC/HDL-C ratio, homocystein, thrombogenic/hemostatic factors, inflammatory markers, impaired fasting glucose, and subclinical atherosclerotic diseases such as ankle-brachial pressure index (ABI), tests for myocardial ischemia, and tests for atherosclerotic plaque burden (i.e., carotid intima medial thickening and coronary calcium).[75] Of these emerging risk factors, apo B occupies a unique position because the presence of apo B in plasma is

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[73] Ibid.

[74] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Ibid.2002;106(25):3143-421.

[75] Ibid.

strongly correlated with the severity of coronary atherosclerosis and CHD events, and it is considered the major apolipoprotein residing within every atherogenic lipoprotein.[76]

Lipid Risk Factors

As mentioned, the most important lipids connected with the atherosclerotic process include high serum levels of LDL-C and TG, and low levels of HDL-C. However, LDL-cholesterol is thought to be the main initiating factor for atherosclerosis and the development of subsequent ASCVD such as CHD (e.g., CAD and ischemic heart disease, IHD) and hypertensive heart disease.[77] Several epidemiological studies such as the Framingham Heart Study,[78] the Multiple Risk Factor Intervention Trial (MRFIT),[79] and the Lipid Research Clinics (LRC) trials,[80] have all found a direct relationship between increased levels of LDL-C (and by implication, TC) and increased rate of incident CHD among men and women. In those with established CHD, the rates of coronary events such as myocardial infarction (MI) or death from cardiovascular disease

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[76] Tornvall P, Bavenholm P, Landou C, de Faire U, and Hamsten A. Relation of plasma levels and composition of apolipoprotein B-containing lipoproteins to angiographically defined coronary artery disease in young patients with myocardial infarction. Ibid.1993;88(5 Pt 1):2180-9; Sedlis SP, Schechtman KB, Ludbrook PA, Sobel BE, and Schonfeld G. Plasma apoproteins and the severity of coronary artery disease. Ibid.1986;73(5):978-86; Gotto AM, Jr., Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Ibid.2000;101:477-84.

[77] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Ibid.2002;106(25):3143-421.

[78] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, and Kannel WB. Prediction of coronary heart disease using risk factor categories. Ibid.1998;97(18):1837-47.

[79] Stamler J, Wentworth D, and Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA. 1986;256(20):2823-8.

[80] The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. Ibid.1984;251(3):351-64; Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984;251:365-74.

are increased with increased levels of LDL-C.[81] Levels of LDL-C above 100mg/dL are believed to be atherogenic, with higher levels posing greater risk of ASCVD.[82]

The Prospective Cardiovascular Munster (PROCAM) study showed that serum triglycerides also is an independent risk factor for CHD events, irrespective of serum levels of HDL-C or LDL-C.[83] Similarly, a meta-analysis of 17 population-based prospective studies of the association between triglycerides and cardiovascular disease showed that elevated serum triglycerides and triglycerides-rich lipoproteins are an independent risk factor of CHD.[84] Factors associated with high TG levels in the body include overweight and obesity, physical inactivity, cigarette smoking, excess alcohol intake, very high carbohydrate consumption (>60% of total energy intake), other diseases (e.g., diabetes, chronic renal failure, nephrotic syndrome), drugs (e.g., corticosteroids, protease inhibitors, β-blockers, estrogens), and genetic factors.[85]

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[81] Rossouw JE, Lewis B, and Rifkind BM. The value of lowering cholesterol after myocardial infarction. N Engl J Med. 1990;323(16):1112-9; Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. Ibid.;322(24):1700-7; Wong ND, Wilson PW, and Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham Study. Ann Intern Med. 1991;115(9):687-93.

[82] Stamler J et al., "Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT)."

[83] Assmann G, Schulte H, Funke H, and von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J. 1998;19 Suppl M:M8-14.

[84] Austin MA, Hokanson JE, and Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol. 1998;81(4A):7B-12B.

[85] Chait A, and Brunzell JD. Acquired hyperlipidemia (secondary dyslipoproteinemias). Endocrinol Metab Clin North Am. 1990;19(2):259-78; Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am. 1994;78(1):117-41.

Strong epidemiological evidence consistently showed that a low level of serum HDL cholesterol is an independent risk factor for CHD.[86] For instance, a 1 percent decrease in serum HDL-C is said to be associated with a 2-3 percent increase in CHD risk.[87] HDL-C is believed, among other mechanisms, to exert its anti-atherogenic effects by promoting efflux of cholesterol from atherosclerotic foam cells,[88] or by inhibiting atherogenesis through their antioxidant and anti-inflammatory effects.[89] Factors associated with low serum HDL-C include elevated serum TG, overweight and obesity, physical inactivity, cigarette smoking, very high carbohydrate consumption (>60% of total energy intake), diabetes, drugs (e.g., β-blockers, anabolic steroids, progestins), and genetic factors.[90]

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[86] Wilson PW et al., "Prediction of coronary heart disease using risk factor categories."; Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Ibid.1989;79(1):8-15; Abbott RD, Donahue RP, Kannel WB, and Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA. 1988;260(23):3456-60; Wilson PW, Garrison RJ, Castelli WP, Feinleib M, McNamara PM, and Kannel WB. Prevalence of coronary heart disease in the Framingham Offspring Study: role of lipoprotein cholesterols. Am J Cardiol. 1980;46(4):649-54; Assmann G, Schulte H, von Eckardstein A, and Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis. 1996;124 Suppl:S11-20.

[87] Gordon DJ et al., "High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies."

[88] Tall AR. An overview of reverse cholesterol transport. Eur Heart J. 1998;19 Suppl A:A31-5.

[89] Van Lenten BJ, Hama SY, de Beer FC, et al. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest. 1995;96(6):2758-67; Navab M, Hama SY, Anantharamaiah GM, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. J Lipid Res. 2000;41(9):1495-508; Navab M, Hama SY, Cooke CJ, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. Ibid.:1481-94.

[90] Stone NJ, "Secondary causes of hyperlipidemia."; Chait A and Brunzell JD, "Acquired hyperlipidemia (secondary dyslipoproteinemias)."; Krauss RM. Regulation of high density lipoprotein levels. Med Clin North Am. 1982;66(2):403-30.

2.1.7 Management of Hyperlipidemia

The following section describes the management of hyperlipidemia based on the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (also known as Adult Treatment Panel III, or ATP III) of the National Cholesterol Education Program.[91] It should be noted, however, that there have been some significant changes to the core elements of the ATP III guidelines with the recent (December 2013) release of the American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol (or the ACC/AHA guideline Expert Panel).[92] The ATP III guideline is used in this discourse because the timeline of the study (2003 – 2004) is based on the recommendations of the ATP III released in 2001. However, comments [mostly in square brackets] will be presented alongside the discourse that highlights the key updates of ATP III that is reflected in the ACC/AHA guidelines (colloquially ATP IV).

Cardiovascular Risk Assessment

According to the ATP III guidelines, the main concept in the management of hyperlipidemia involves the targeting of LDL-C in particular, and engagement in patient risk assessment to determine the appropriate lipid goals for the different classes of cardiovascular risks [The ATP III uses LDL–C and/or HDL–C levels to target treatment,

[91] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.

[92] Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.

and evaluates the 10-year cardiovascular risk using the Framingham risk score, while the ATP IV guidelines now recommend that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit, and estimates the 10-year ASCVD risk using the new Pooled Cohort Equations.[93]] Studies showed that the risk of CHD is estimated to be reduced by 1% for every 1% reduction in LDL-C.[94] This is because LDL-C reduction improves cardiovascular protection by increasing the rate of plaque regression and stabilization. More aggressive treatment is therefore recommended for patients at increased risk than patients at lower CHD risk.

Other major risk factors, exclusive of LDL-C that modifies LDL goals include: family history of premature CHD (i.e., myocardial infarction or sudden death before age 55 in a first degree relative of the male sex, or before age 65 in a first degree relative of the female sex); cigarette smoking; hypertension (systolic and diastolic blood pressure, BP ≥140/90 mmHg, or presently taking antihypertensive medication); age ≥45 years in men or ≥55 years in women; diabetes mellitus; HDL-C below 40mg/dL in men and below 50mg/dL in women.[95] Table 2.1 summarizes the categories of risk factors modifying LDL-C goals in dyslipidemic patients based on the ATP III guideline [ATP IV

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[93] American College of Cardiology and American Heart Association. ASCVD risk estimator. 2014; Available at: http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp. Accessed 5/22, 2014.

[94] Cannon CP et al., "Intensive versus moderate lipid lowering with statins after acute coronary syndromes."; Pedersen TR et al., "High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial."; Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. Ibid.2001;285(13):1711-8.

[95] Angelico F et al., "Current ways of treating dyslipidemias to prevent atherosclerosis."; "Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)."

guideline now focuses on treatment of blood cholesterol to reduce ASCVD risk. Four statin benefit groups were identified (with less focus on treating to LDL-C target) in which the potential for an ASCVD risk reduction benefit clearly exceeds the potential for adverse effects. The four statin benefit groups are presented in Table 2.2].

Table 2.1: Categories of Risk that Modify LDL-Cholesterol Goals in the ATP III Guideline

Risk Category	Number of Risk Factors[a]	Target LDL-C (mg/dL)
Low risk	0 – 1	<160
Moderate risk	>2	<130
High risk	CHD or CHD-risk equivalent[b]	<100
Very high risk	CHD + DM + MetS or ACS	<70

Source: Angelico F, Baratta F, Del Ben M. Current ways of treating dyslipidemias to prevent atherosclerosis. *Ther Apher Dial.* 2013;17(2):125-129.
Abbreviations: LDL-C, Low-density lipoprotein cholesterol; CHD, Coronary heart disease; MetS, Metabolic syndrome; ACS, Acute coronary syndrome; DM, Diabetes mellitus.
[a]Risk factors include family history of premature CHD, cigarette smoking, BP ≥140/85, HDL-C less than 40mg/dL (men) and 50mg/dL (women).
[b]CHD-risk equivalent include ACS, peripheral artery disease, abdominal aortic aneurysm, cerebrovascular disease, and DM.

Table 2.2: ASCVD Risk Reduction in 4 Statin Benefit Groups in the ATP IV Guideline	
Group	**Clinical Characteristics**
1	Individuals with clinical ASCVD (acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin) without New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis
2	Individuals with primary elevations of LDL–C ≥190 mg/dL
3	Individuals 40 to 75 years of age with diabetes with LDL-C 70-189 mg/dL
4	Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

Source: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-934.

Treatment of Hyperlipidemia

ATP III recommends a periodic testing of all adults for dyslipidemia beginning at age 20. In the ATP III guideline for the treatment of hyperlipidemia (Table 2.3), LDL-C lowering medication is chosen based on patients' LDL-C level and their CHD risk category estimated using the Framingham risk score.[96] The focus of the new ATP IV guideline (Table 2.4), however, is in choosing the appropriate intensity level of statin

[96] Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, and Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.

(defined in Table 2.5) for the reduction of blood cholesterol in the primary and secondary prevention of ASCVD in adults. The recommended statin intensity depends on such factors as the patient's age, level of LDL-C, and the presence or absence of diseases such as clinical ASCVD and diabetes mellitus.[97] Rather than using the Framingham risk score to determine patient's CHD risk category, ATP IV now uses a 'new Pooled Cohort Equation' to estimate the 10-year ASCVD risk in men and women who do not have clinical ASCVD.[98]

In both guidelines, however, the therapeutic management of hyperlipidemia involves the use of pharmacological and non-pharmacological strategies. Non-pharmacological strategies include therapeutic lifestyle changes (TLC) diets, increased physical activity, and smoking cessation. Pharmacological strategy involves the use of lipid-lowering drugs, especially statins. [ATP IV still recommends therapeutic lifestyle modifications as a critical component of health promotion and ASCVD risk reduction, both prior to, and in concert with the use of cholesterol-lowering drug therapies].[99]

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[97] Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."
[98] American College of Cardiology and American Heart Association, "ASCVD risk estimator".
[99] Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

Table 2.3: Management of LDL Cholesterol in Persons with Different CHD Risk Categories in the ATP III Guideline				
Risk category	**Patient's LDL-C Level (mg/dL)**	**LDL-C Goal (mg/dL)**	**Level of LDL-C at which to Initiate TLC (mg/dL)**	**Level of LDL-C at which to Initiate LDL-lowering Drugs (mg/dL)**
CHD or CHD-risk equivalent	≥130	<100	≥100	Start drug therapy simultaneously with dietary therapy
	100-129	<100	≥100	Consider drug option
	<100	<100	TLC & emphasize weight control and physical activity	LDL-lowering drugs not required
Multiple (2+) risk factors	**10-year risk for CHD**			
	>20%	<100	≥100	Start drug therapy simultaneously with dietary therapy
	10-20%	<130	≥130	≥130
	<10%	<130	≥130	≥160
0-1 risk factor[a]		<160	≥160	≥190[b]

Source: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.
Abbreviations: LDL-C, Low-density lipoprotein cholesterol; TLC, Therapeutic lifestyle changes; CHD, Coronary heart disease.
[a]Most persons with 0–1 risk factor have a 10-year risk for CHD of <10 percent.
[b]Drug therapy is optional for LDL-C of 160–189 mg/dL (after dietary therapy).

Table 2.4: Management of Hyperlipidemia to Reduce ASCVD Risk in the ATP IV Guideline						
ASCVD Prevention	**Age (years)**	**LDL-C (mg/dL)**	**Has diabetes?**	**Has clinical ASCVD?**	**10-year ASCVD risk (%)**	**Recommended statin intensity**
Primary	≥21	≥190[a]	No	No	Not required	High[b]
	40-75	70-189	Yes	No	<7.5	Moderate[c]
	<40 or >75	70-189	Yes	No	Not specified	Not specified[d]
	40-75	70-189	No	No	≥7.5	Moderate/High[e]
	40-75	70-189	No	No	5.0 to <7.5	Moderate/High[e]
Secondary	≤75	Any level	No	Yes	-	High[f]
	>75	Any level	No	Yes	-	Moderate/High[g]

Source: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-934.

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; LDL-C, Low-density lipoprotein cholesterol.

[a]Or has TG≥500mg/dL.

[b]Evaluate for secondary causes of hyperlipidemia.Use maximum tolerated statin dose for those intolerant of high-intensity dose. Intensify dose to achieve at least a 50% LDL-C reduction. May consider adding a non-statin drug to further lower LDL-C.

[c]Consider high-intensity statin if 10-year ASCVD risk is ≥7.5%.

[d]Evaluate benefit of ASCVD risk-reduction versus potentials for adverse effects and drug-drug-interactions. Consider patient preferences when deciding to initiate, continue, or intensify therapy.

[e]Evaluate benefit of ASCVD risk-reduction versus potentials for adverse effects and drug-drug interactions. Consider patient preferences.

[f]Use moderate-intensity statin if intolerant to high-intensity statin.

[g]When using high-intensity dose, evaluate benefit of ASCVD risk-reduction versus potentials for adverse effects and drug-drug interactions. Consider patient preferences. Continue therapy if tolerated.

Table 2.5: Statin Intensity Dosage Levels as Defined in the New ATP IV Guideline			
Statin	**Low-Intensity Dose (mg)**	**Moderate-Intensity Dose (mg)**	**High-Intensity Dose (mg)**
Atorvastatin	-	10, 20	40-80
Fluvastatin	20-40	40mg bid, 80 (XL)	-
Lovastatin	20	40	-
Pitavastatin	1	2-4	-
Pravastatin	10-20	40, 80	-
Rosuvastatin	-	5, 10	20, 40
Simvastatin	10	20-40[a]	-
Approximate % of LDL-C lowered by daily dose	<30%	30% to <50%	≥ 50%

Source: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-934.
Abbreviations: bid, twice daily; XL, Extended release dosage form; LDL-C, Low-density lipoprotein cholesterol.
[a]Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Non-Pharmacological Management

As mentioned earlier, the ATP IV still recommends the use of non-pharmacological therapeutic lifestyle changes as a critical component of health promotion and ASCVD risk reduction.[100] Unfortunately, the use of non-pharmacological TLC alone is usually not adequate for reaching target lipid levels in many patients, thus necessitating the addition of lipid-lowering medications.[101] TLC regimen that can be used both prior to, and in concert with the use of cholesterol-lowering drug therapies include weight management, increased physical activity, smoking cessation, and TLC diets that are low in sodium, saturated fat and total cholesterol, but high in fiber. Table 2.6 provides a summary of the essential components of the NCEP/ATP III-recommended TLC regimen.

[100] Ibid.
[101] "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report."

Table 2.6: NCEP/ATP III-Recommended Therapeutic Lifestyle Changes (TLC) Regimen	
Component	**Recommendations**
LDL-raising nutrients	
Saturated fats[a]	<7% of total calories
Dietary cholesterol	<200 mg/day
Therapeutic options for LDL-lowering	
Plant stanols/sterol	2g per day
Viscous/soluble fiber	10-25g per day
Total calories (energy)[b]	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain
Physical activity	30 minutes of regular moderate intensity activity on most, if not all, days of the week[c]
Body weight	10% weight loss goals for overweight persons
Smoking cessation	Employ pharmacological and non-pharmacological strategies to smoking cessation
Macronutrient recommendations for the TLC diet	
Total fat	25% to 35% of total calories
Polyunsaturated fat	≤10% of total calories
Monounsaturated fat	≤20% of total calories
Carbohydrates[d]	50% to 60% of total calories
Fiber	20-30 g/day
Protein	~15% of total calories

Source: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.

[a]*Trans* fatty acids (partially hydrogenated oils) intake should be kept low. These are found in potato chips, other snack foods, margarines and shortenings, and fast-foods.

[b]Daily energy expenditure should include at least moderate physical activity.

[c]Based on patient's cardiac status, age and other factors.

[d]Complex carbohydrates, including grains (especially whole grains, fruits, and vegetables).

Pharmacological Management

Currently, five classes of drugs are available for the treatment of dyslipidemia.[102] They include:

- Statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin);
- Bile-acid sequestrants (cholestyramine, colesevelam and colestipol);
- Fibrates (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil);
- Nicotinic acid or niacin; and
- Ezetimibe.

The patient's lipid profile, concomitant disease states, and the cost of therapy are some of the factors that needed to be considered when choosing drug therapy for the patient. Before the new ATP IV guideline was released, the patient's overall lipid profile level (including LDL-C, HDL-C, and TG levels) informed the selection of pharmacotherapy using either statin monotherapy or combination therapy of statins and non-statin lipid-lowering agents (Table 2.7). [In the new ATP IV guideline, however, the selection of the appropriate level of statin intensity needed to prevent ASCVD is primarily based on the patient's LDL-C level, with less emphasis placed on levels of HDL-C and TG. Furthermore, the use of non-statin lipid lowering medications may be recommended if the ASCVD risk-reduction benefits outweigh the potential for adverse

[102] Fischer S, Schatz U, and Julius U. Current standards in diagnosis and therapy of hyperlipoproteinemia. Atheroscler Suppl. 2013;14(1):15-8; "Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)."

effects: 1) in candidates for statin therapy who are statin-intolerant; and 2) in patients with high ASCVD risk (i.e., individuals with clinical ASCVD and age <75 years, individuals with baseline LDL-C ≥190mg/dL, and individuals aged 40-75 years with diabetes mellitus) who are receiving the maximum tolerated intensity of statin therapy but with inadequate therapeutic outcome].[103] Table 2.8 gives a summary of the advantages and disadvantages of currently available lipid-lowering drugs, including their modes of action.

Table 2.7: Lipid-Lowering Drug Selection Process in the ATP III Guideline

Lipid Profile	Monotherapy	Combination Therapies
High LDL-C[a] + Normal HDL[b] + Normal TG[c]	BAS or Niacin[d] or Statin	BAS + Niacin[d] or BAS + Statin or Statin + Niacin[d,e]
High LDL-C + High TG[e]	Intensify LDL-lowering therapy	Statin + Niacin[d,f] or Statin + Fibrates[f]
High LDL-C + High TG (≥500 mg/dL)[e]	Consider a combination therapy from Niacin,[d] Fibrates, and Statin	
High TG	Niacin[d] or Fibrates	Niacin[d] + Fibrates
High LDL-C + Low HDL-C	Niacin[d] or Statin	Statin + Niacin[d,e]

Source: Hyperlipidemia management. Lexicomp Online; 2013.
Abbreviations: LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; TG, Triglycerides; BAS, Bile-acid sequestrants.
[a]LDL-C <100mg/dL = optimal; 100-129mg/dL = near optimal; 130-159mg/dL = borderline high; 160-189mg/dL = high; ≥190mg/dL = very high.
[b]HDL-C <40mg/dL = low; ≥60mg/dL = high or optimal.
[c]TG <150mg/dL = normal; 150-199mg/dL = borderline high; 200-499mg/dL = high; ≥500mg/dL = very high.
[d]Avoid in diabetics.
[e]Emphasize weight reduction and increased physical activity.
[f]Risk of myopathy increases with combination.

[103] Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

Table 2.8: Advantages, Disadvantages, and Modes of Action of Lipid-Lowering Therapeutic Agents			
Agent	**Mechanism of Action**	**Advantages**	**Disadvantages**
HMG-CoA reductase inhibitors or statins: -atorvastatin (Lipitor®) -fluvastatin (Lescol®) -lovastatin (Mevacor®) -pitavastatin (Livalo®) -pravastatin (Pravachol®) -rosuvastatin (Crestor®) -simvastatin (Zocor®)	They inhibit HMG-CoA reductase enzyme, which is the rate limiting step of cholesterol synthesis in the liver	-Produces greatest LDL-C reduction -Generally well-tolerated with convenient once a day dosing -Proven decrease in CVD morbidity and mortality	Relatively expensive
Bile acid sequestrants: -cholestyramine (Questran®) -colesevelam (Welchol®) -colestipol (Colestid®)	Through disruption of bile-acid enterohepatic circulation, they prevent the reabsorption of bile-acids from the gut[a]	-Good choice for those with high LDL-C levels -Decreases LDL-C up to 50% when combined with a statin -Has low potential for systemic side effects -Good choice for younger patients	-May increase TG -High potentials for adverse effects and drug interactions -Moderately expensive -Inconvenient dosing
Niacin (Niaspan®) (also known as vitamin B_3 or nicotinic acid)	Through their hydroxyl carboxylic acid receptor, they inhibit lipolysis and free fatty acids available for liver production of TG, VLDL-C and consequently LDL-C	-Good choice for almost any lipid abnormality -Inexpensive -Greatest increase in HDL-C	-High incidence of adverse effects -May adversely affect diabetes (with high dose >1.5 g/day) and gout -Niacin ER may not increase HDL-C or decrease TG as well as immediate release niacin

Table 2.8: Advantages, Disadvantages, and Modes of Action of Lipid-Lowering Therapeutic Agents (Cont'd)			
Agent	**Mechanism of Action**	**Advantages**	**Disadvantages**
Fibric acid derivatives -bezafibrate (Bezalip®)[b] -ciprofibrate (Modalim®)[c] -clofibrate[d] -fenofibrate (Tricor®) -gemfibrozil (Lopid®)	-Induces lipoprotein lipolysis -Enhances hepatic fatty acid uptake and reduction of hepatic TG production -Causes increased removal of LDL particles	Good choice in patients with high TG levels where niacin is contraindicated or not well tolerated	Variable effects on LDL-C
Ezetimibe (Zetia®)	Decreases intestinal absorption of cholesterol	Produces additional cholesterol-lowering effects when combined with statins	Effects similar to bile acid sequestrants
Lomitapide (Juxtapid®)[e]	Inhibits the microsomal triglyceride transfer protein necessary for liver assembly and secretion of VLDL	-Decreases LDL-C up to 50% when combined with a statin -Decrease TG levels	Produces high incidence of gastrointestinal adverse effects, especially if used with high-fat diet

Source: Hyperlipidemia management. Lexicomp Online; 2013.

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl Coenzyme A; LDL-C, Low-density lipoprotein cholesterol; CVD, Cardiovascular disease; TG, Triglycerides; VLDL-C, Very low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; ER, Extended release.

[a]Bile acids are biosynthesized from cholesterol; thus, disruption of bile acid reabsorption will decrease cholesterol levels.

[b]Canada brand. Drug is not currently available in the US.

[c]Great Britain brand. Drug is not currently available in the US.

[d]Discontinued in 2002 due to adverse effects.

[e]Approved by the FDA in December 2012 as an orphan drug to reduce LDL-C, total cholesterol, and apolipoprotein B in patients with homozygous familial hypercholesterolemia.

2.2 SECTION II: STATINS

2.2.1 History

Early research on statin and cholesterol synthesis was attributed to Drs. Akira Endo and Masao Kuroda (who isolated the first non-commercial statin called compactin, and later renamed mevastatin, from cultures of the fungi *Penicillium citrinum* in 1976),[104] and two scientists, Drs. Joseph Goldstein and Michael Brown, who were awarded the Nobel Prize in Physiology or Medicine in 1985 for their work on cholesterol synthesis inhibition and the subsequent development of statin drugs.[105] Two years later, lovastatin was developed by Merck, and became the first statin to be approved by the US Food and Drug Administration (FDA) in 1987.[106] Over the next two and one half decades, the FDA granted approval to seven other statins that were either derived from fungi (i.e., pravastatin and simvastatin), or were synthetically manufactured (i.e., fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin).[107] All the aforementioned statins are currently approved for use in the US except cerivastatin. Cerivastatin (Baycol® and Lipobay®) was withdrawn from the US market in August 2001 by the manufacturer, Bayer.[108] The withdrawal was due to several increasing reports of rhabdomyolysis, a

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[104] Endo A, Kuroda M, and Tsujita Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by Penicillium citrinium. J Antibiot (Tokyo). 1976;29(12):1346-8.
[105] Brown MS, Faust JR, Goldstein JL, Kaneko I, and Endo A. Induction of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in human fibroblasts incubated with compactin (ML-236B), a competitive inhibitor of the reductase. J Biol Chem. 1978;253(4):1121-8.
[106] Baliga RR. Statin prescribing guide. Vol. ed. Oxford: Oxford University Press, USA; 2010.
[107] Ibid.; Mukhtar RY, Reid J, and Reckless JP. Pitavastatin. Int J Clin Pract. 2005;59(2):239-52.
[108] U.S. Food and Drug Administration. Safety: Baycol (cerivastatin sodium tablets) Aug 2001. 2001; Available at:

severe form of muscle breakdown that may lead to acute renal failure.[109] Table 2.9 and Table 2.10 present the currently available statins and statin combination products in the US, respectively.

Table 2.9: Currently Available Statins in the United States

Statin	Year Approved	Brand Name	Applicant	First Generic Available	Other Brands
Lovastatin	1987	Mevacor®	Merck	2001	Altoprev®
Pravastatin	1991	Pravachol®	Bristol-Myers Squibb	2006	NA
Simvastatin	1991	Zocor®	Merck	2006	NA
Fluvastatin	1993	Lescol®	Novartis	2012	NA
Atorvastatin	1996	Lipitor®	Pfizer	2011	NA
Rosuvastatin	2003	Crestor®	AstraZeneca	NA	NA
Pitavastatin	2009	Livalo®	Kowa Co.	NA	NA
Cerivastatin	1998[a]	Baycol®, Lipobay®	Bayer A.G.	NA	NA

Source: US Food and Drug Administration. Orange Book: Approved drug products with therapeutic equivalence evaluations; 2013.
[a]Withdrawn from the US market in 2001.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172268.htm. Accessed June 22, 2014.

[109] Lucas RA, Weathersby BB, Rocco VK, Pepper JM, and Butler KL. Rhabdomyolysis associated with cerivastatin: six cases within 3 months at one hospital. Pharmacotherapy. 2002;22(6):771-4; Staffa JA, Chang J, and Green L. Cerivastatin and reports of fatal rhabdomyolysis. N Engl J Med. 2002;346(7):539-40.

Table 2.10: Currently Available Statin Combination Products in the United States			
Drug	**Brand Name**	**Generic Available?**	**Applicant**
Lovastatin + niacin	Advicor®	No	Abbvie
Simvastatin + sitagliptin	Juvisync®	No	MSD
Simvastatin + ezetimibe	Vytorin®	No	MSD Intl
Simvastatin + niacin	Simcor®	No	Abbvie
Atorvastatin + amlodipine	Caduet®	Yes	Pfizer
Atorvastatin + ezetimibe	Liptruzet®	No	Merck

Source: US Food and Drug Administration. Orange Book: Approved drug products with therapeutic equivalence evaluations; 2013.
Abbreviations: MSD, Merck Sharp Dohme.

2.2.2 Statin Utilization and Spending in the United States

In the US, statins are among the most widely prescribed therapeutic class of drugs, with simvastatin (86.1 million) and atorvastatin (54.9 million) alone accounting for over 140 million dispensed prescriptions in 2012.[110] Moreover, the best-selling statin used to be atorvastatin, marketed as Lipitor® by Pfizer. However, due to the loss of Lipitor® patent in November 30, 2011, the US non-discounted spending on atorvastatin (Lipitor® included) decreased to $2.3 billion in 2012. This amount is in contrast to $7.7 billion of non-discounted spending that was attributed to Lipitor® alone in 2011.[111] Crestor®, a rosuvastatin brand marketed by AstraZeneca currently has the largest share of non-discounted spending, with $5.1 billion in sales in 2012.[112]

2.2.3 Pharmacokinetic and Pharmacodynamic Properties

The HMG-CoA (3-hydroxy-3-methylglutaryl Co-enzyme A) reductase inhibitors – commonly referred to as statins – have the same pharmacophore, which is a modified hydroxyglutaric acid component that is structurally similar to the endogenous substrate HMG-CoA on which they exert their effect.[113] However, modification of the general ring structure confers on each statin a unique ring structure and substituents which considerably make their physicochemical properties (e.g., solubility, lipophilicity) differ. This in turn affects their pharmacokinetics (e.g., bioavailability, tissue distribution,

[110] IMS Health Incorporated. Top-line market data. 2013; Available at: http://www.imshealth.com/portal/site/ims/menuitem.5ad1c081663fdf9b41d84b903208c22a/?vgnextoid=fbc65890d33ee210VgnVCM10000071812ca2RCRD&vgnextfmt=default. Accessed 8/27, 2013.
[111] Ibid.
[112] Ibid.
[113] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19(1):117-25.

protein binding, renal excretion, half-life), and pharmacodynamic properties (e.g., potency, efficacy, toxicity, adverse effect).[114] Most statins have a generally low absolute bioavailability in the systemic circulation. This is indicative of their extensive first-pass metabolism in the liver. However, given that the liver is the target organ for statins, efficient first-pass uptake by the liver may be more important than high systemic bioavailability for statins to exert their anti-lipemic effects.[115] Table 2.11 presents a summary of the pharmacokinetic properties of currently available statins.

[114] Ibid.
[115] Ibid.

Table 2.11: Pharmacokinetic Properties of Currently Available Statins							
	Lovastatin	**Pravastatin**	**Simvastatin**	**Fluvastatin**	**Atorvastatin**	**Rosuvastatin**	**Pitavastatin**
Lipophilicity	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic
Absolute bioavailability (%)	<5	17	<5	24 29 (ER)	~14	~20	51[a]
Mean peak plasma concentration (hrs)	2-4 14 (ER)	1-5	4	1 3 (ER)	1-2	3-5	1
Onset of action (weeks)	2	1-4	4-6	2-4	2-4	4	1-4
Optimal time of dosing	Evening (IR) Bedtime (ER)	Bedtime	Evening	Bedtime	Any time of day	Any time of day	Any time of day
Effects of food on AUC	Decreased	Decreased	Not significant	Decreased	Not significant	Not significant	Not significant
Protein binding (%)	>95	~50	95	~98	≥98	88	>99
CYP450 metabolism? Isoenzyme	Yes CYP3A4	No	Yes CYP3A4	Yes CYP2C9	Yes CYP3A4	Yes CYP2C9	Limited UGT1A1
Active metabolites?	Yes	No	Yes	Yes	Yes	Yes	No
Elimination route **Urine (%)** **Feces (%)**	 10 83	 20 70	 13 60	 5 90	 <2 >98	 10 90	 15[a] 79[a]
Half-life (hours)	0.5-3	1.8	0.5-3	<3 9 (ER)	~14	~19	~12

Sources: Lexicomp Online; 2013. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol.* 2005;19(1):117-125.

Abbreviations: ER, Extended release tablet or capsule; IR, Immediate release tablet or capsule; AUC, Area under the concentration vs. time Curve; CYP450, Cytochrome P-450 enzyme system; UGT, Uridine 5´-diphosphate glucuronosyltransferase enzyme system.

[a]Evaluated in oral solution that is not commercially available in the US.

2.2.4 Mechanism of Action

Figure 2.1 graphically summarizes the major sites of action of statin in the cholesterol biosynthetic pathway. Statins reduce atherogenic lipoproteins primarily through competitive inhibition of HMG-CoA reductase.[116] HMG-CoA reductase is an enzyme necessary for the conversion of HMG-CoA to mevalonate. The inhibition of mevalonate production is the rate-limiting step in the synthesis of cholesterol in the liver. Statins also exhibit their anti-lipemic actions through several secondary mechanisms of action that include "up-regulation" of the LDL-C receptor.[117] The LDL-C receptor is the membrane receptor which recognizes, binds, and internalizes the circulating apolipoproteins which carry apo-B and apo-E on their surface. The LDL-C receptor up-regulation leads to plasma clearance of cholesterol-rich LDL-C and, to a lesser extent, VLDL-C and IDL-C.[118] Other statin actions include the reduction in hepatic synthesis and secretion of TG-rich lipoproteins,[119] elevation of HDL-C, and inhibition of the Rho/Rho Kinase signaling pathway – an action believed to inhibit the development of the atherosclerosis process.[120]

In addition to their anti-lipemic effects, statins also exert beneficial cardiovascular effects which are independent of their lipid-lowering effects. These additional properties, known as statin pleiotropic effects, are believed to improve endothelial function, stabilize

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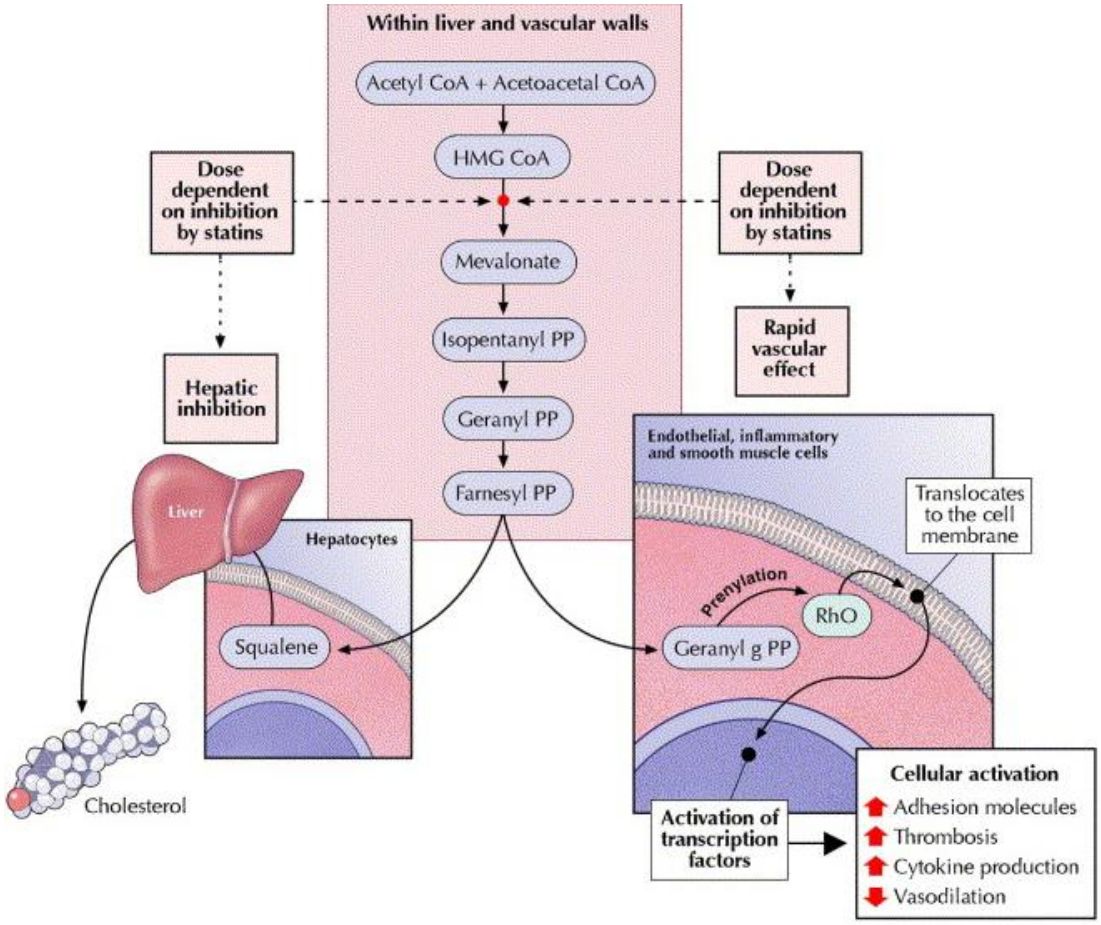
[116] Baliga RR, *Statin prescribing guide*.
[117] Ibid.
[118] Ibid.
[119] Grundy SM. Consensus statement: Role of therapy with "statins" in patients with hypertriglyceridemia. Am J Cardiol. 1998;81(4A):1B-6B.
[120] Baliga RR, *Statin prescribing guide*.

atherosclerotic plaque, improve nitric oxide availability, decrease vascular inflammatory responses, and reduce smooth muscle proliferation and cholesterol accumulation.[121]

Figure 2.1: Inhibition of Cholesterol Synthesis by Statins



Source: Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol.* 2005;46(8):1425-1433.
Abbreviations: HMG CoA, 3-hydroxy-3-methylglutaryl Coenzyme A; PP, pyrophosphate.

[121] Ibid.; Ray KK, and Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. J Am Coll Cardiol. 2005;46(8):1425-33.

2.2.5 Primary and Secondary Prevention of Cardiovascular Diseases

Cardiovascular disease (e.g., CAD, CHD, and IHD) – which include a spectrum of diagnoses including angina pectoris, myocardial infarction, acute coronary syndrome, and sudden cardiac death – is one of the leading causes of death in the world and the United States.[122] The high morbidity and mortality resulting from cardiovascular disease impose a heavy economic burden on America, and also negatively impacts the quality of life of Americans living with cardiovascular disease (CVD).[123]

The aim of primary prevention using statins is to prevent the incidence of CHD through reduction of the risk factors associated with CHD. In contrast, the aim of secondary prevention is to reduce the incidence and prevalence of recurrent CHD in people with established CHD.[124] The prevalence of CHD is high among Americans due to a combination of cholesterol-rich diets and CVD risk factors such as hypertension, tobacco use, diabetes, obesity, physical inactivity, and increasing age.[125]

Primary and secondary prevention of dyslipidemia and CVD can be achieved by therapeutic lifestyle changes, use of LDL-lowering drugs, or both;[126] however, differing results of LDL-C lowering is achieved depending on the method or combination of methods employed.

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[122] Roger VL et al., "Heart disease and stroke statistics--2012 update: a report from the American Heart Association."
[123] Chen J, and Rizzo JA. The economics of cardiovascular disease in the United States. Crit Care Clin. 2012;28(1):77-88.
[124] "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report."
[125] Graham I et al., "Dyslipidemias in the prevention of cardiovascular disease: risks and causality."
[126] Angelico F et al., "Current ways of treating dyslipidemias to prevent atherosclerosis."

2.2.6 Efficacy of Therapeutic Lifestyle Changes

Serum cholesterol lowering through dietary modification has been demonstrated through several primary[127] and secondary[128] prevention trials. Overall, these trials showed a positive trend of the efficacy of dietary modification to lower serum cholesterol. Furthermore, attestation to the effectiveness of lifestyle changes such as smoking cessation, increased physical activity, modification of diet, and weight reduction on reducing serum cholesterol are the basis for several evidence-based public health recommendations and guidelines, including the US Surgeon General's Reports on Health Consequences of Smoking,[129] Physical Activity Guidelines for Americans,[130] Clinical Guidelines on Overweight and Obesity,[131] and Dietary Guidelines for Americans.[132] The

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[127] Hjermann I, Velve Byre K, Holme I, and Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet. 1981;2(8259):1303-10; Frantz ID, Jr., Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. Arteriosclerosis. 1989;9(1):129-35; Miettinen M, Turpeinen O, Karvonen MJ, Elosuo R, and Paavilainen E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes. A twelve-year clinical trial in men and women. Lancet. 1972;2(7782):835-8; The multiple risk factor intervention trial (MRFIT). A national study of primary prevention of coronary heart disease. JAMA. 1976;235(8):825-7.

[128] Ball KP, Hanington E, McAllen PM, et al. Low-fat diet in myocardial infarction: a controlled trial. Lancet. 1965;2:501-4; Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Acta Med Scand Suppl. 1966;466:1-92.

[129] U.S. Department of Health and Human Services. "The Health Consequences of Smoking: A Report of the Surgeon General." 941 pages. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

[130] U.S. Department of Health and Human Services. "Physical Activity Guidelines for Americans." 76 pages. Washington, DC., 2008.

[131] National Institutes of Health. "Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults - the evidence report." 228 pages. Bethesda, MD: National Heart, Lung and Blood Institute, 1998; Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--The Evidence Report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51S-209S.

[132] U.S. Department of Agriculture and U.S. Department of Health and Human Services. "Dietary Guidelines for Americans." 112 pages. Washington, DC: U.S. Government Printing Ofice, 2010.

NCEP/ATP III and the recently released ATP IV guidelines also affirm the validity of therapeutic lifestyle changes as the first-line therapy for primary and secondary prevention of dyslipidemia and cardiovascular diseases.[133]

2.2.7 Efficacy of Statins in Primary Prevention

Several historic clinical trials have been conducted to examine the efficacy of statins and other non-statin lipid lowering drugs. Before the advent of statins, positive, but limited trends of major coronary events reduction were achieved by landmark clinical trials of non-statin drugs including clofibrate, gemfibrozil, and cholestyramine in the World Health Organization clofibrate trial,[134] the Helsinki Heart Study gemfibrozil trials,[135] and the Lipid Research Clinics cholestyramine trials,[136] respectively. The superiority of statins at reducing LDL-C and relative risks of major coronary events,

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133 "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report."; Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

134 A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. Br Heart J. 1978;40(10):1069-118.

135 Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317(20):1237-45; Huttunen JK, Manninen V, Manttari M, et al. The Helsinki Heart Study: central findings and clinical implications. Ann Med. 1991;23(2):155-9; Huttunen JK, Heinonen OP, Manninen V, et al. The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. J Intern Med. 1994;235(1):31-9.

136 "The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease."; "Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering."

coronary mortality, and all-cause cardiovascular mortality has subsequently been demonstrated in several statin primary prevention trials.[137]

Of the seven currently available statins, the LDL-C lowering efficacies of five statins – atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin – have been widely studied, while efficacy trials involving fluvastatin and pitavastatin are limited. The first major primary prevention statin trial – the West of Scotland Coronary Prevention Study (WOSCOPS) – demonstrated that a 40mg daily dose of pravastatin given to hypercholesterolemic men aged 45-64 years was able to decrease mean LDL-C by 26%; while major coronary events, coronary mortality, and all-cause mortality were decreased by 31 percent, 33 percent, and 22 percent, respectively.[138]

The second major primary prevention statin trial – the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS) – was not as successful as

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[137] Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."; Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."; Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). Ibid.2002;288(23):2998-3007; Shepherd J et al., "Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial."; Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Ibid.2003;361(9364):1149-58; Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Ibid.2004;364(9435):685-96; Knopp RH, d'Emden M, Smilde JG, and Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006;29(7):1478-85; Nakamura H et al., "Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial."; Ridker PM et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein."

[138] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. Ibid.1995;333(20):1301-7.

WOSCOP, recording only significant decreases in mean LDL-C and major coronary events, but a non-significant difference in the number of coronary mortality between the treatment and placebo groups.[139] In general, results from a majority of the primary prevention statin trials provide robust evidence to show that statins have high efficacy at reducing atherogenic lipoproteins such as LDL-C, TC, and TG. Statins have also been shown to be efficacious at reducing the relative risk for major cardiovascular outcomes while minimally increasing the levels of HDL-C, the anti-atherogenic lipoprotein. Table 2.12 provide a summary of the major (i.e., large number of participants followed up for a relatively long period of time) primary prevention trials of statins. Table 2.13 and Table 2.14 give a summary of the effects of statin treatment and lipid-lowering agents, respectively, on lipid profiles.

[139] Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."

Table 2.12: Major Primary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality										
Trials	**Dates**	**Follow-up (years)**	**N**	**Treatment Dose/day**	**Control**	**Baseline LDL-C (mg/dL)[a]**	**LDL-C Change (%)[b]**	**Major Coronary Events (%)[c]**	**Coronary Mortality (%)**	**All-cause Mortality (%)**
WOSCOPS[d]	1989-1995	4.9	6,595	Prava 40mg	Placebo	192	-26*	-31*	-32*	-22*
AFCAPS/ TexCAPS[e]	1990-1997	5.2	6,605	Lova 20-40mg	Placebo	150	-23*	-37*	NS	NS
ALLHAT-LLT[f]	1994-2002	4.8	10,355	Prava 40mg	Usual Care	146	-29*	NS	NS	NS
PROSPER[g]	1997-2001	3.2	5,804	Prava 40mg	Placebo	147	-34*	-15*	-24*	NA
ASCOT-LLA[h]	1998-2002	3.3	10,305	Atorva 10mg	Placebo	132	-32*	-36*	NS	NS
CARDS[i]	1997-2003	3.9	2,838	Atorva 10mg	Placebo	117	-31*	-37*	NA	NS
MEGA[j]	1994-2004	5.3	7,832	Prava 10-20mg + diet	Diet + Usual Care	157	-18*	-33*	NS	NS
ASPEN[k]	1996-2003	4.0	2,410	Atorva 10mg	Placebo	114	-29*	NS	NS	NA
JUPITER[l]	2003-2008	1.9	17,802	Rosuva20 mg	Placebo	108	-49*	-44*	-47*	-20*
HYRIM[m]	NA	4	568	Fluva 40mg	Placebo	150	-22*	-0.029#	NS	NS

Table 2.12: Major Primary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality (Cont'd)

Source: Kizer JR, Madias C, Wilner B, et al. Relation of different measures of low-density lipoprotein cholesterol to risk of coronary artery disease and death in a meta-regression analysis of large-scale trials of statin therapy. *Am J Cardiol.* 2010;105(9):1289-1296; Published articles for each trial results; and TrialResultsCenter.org.

Abbreviations: LDL-C, Low-density lipoprotein cholesterol; NS, Not statistically significant; NA, Not applicable; Atorva, Atorvastatin; Fluva, Fluvastatin; Lova, Lovastatin; Prava, Pravastatin; Rosuva, Rosuvastatin.

*Relative risk reduction is statistically significant at $p<0.05$.

#Absolute risk reduction is statistically significant at $p<0.05$.

[a]Mean baseline LDL-C for the whole group.

[b]LDL-C percentage change from baseline to follow-up for treatment only.

[c]Major coronary events include fatal and non-fatal myocardial infarction or stroke, coronary revascularization, coronary artery bypass surgery, and unstable angina.

[d]Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. WOSCOP Study Group. *N Engl J Med.* 1995;333(20):1301-1307 [**WOSCOPS**, West of Scotland Coronary Prevention Study: West of Scotland and Glasgow, men, hypercholesterolemic, aged 45-64 years].

[e]Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA.* 1998;279(20):1615-1622 [**AFCAPS/TexCAPS**, Air Force/Texas Coronary Atherosclerosis Prevention Study: Texas, 2 sites – Lackland Air Force Base in San Antonio and University of North Texas Health Science Center in Fort Worth, men aged 45-73 years, and women aged 55-73 years].

[f]Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The ALLHAT-LLT. *JAMA.* 2002;288(23):2998-3007 [**ALLHAT-LLT**, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: US, Puerto Rico, US Virgin Islands, and Canada, 513 sites, men and women, moderately hypercholesterolemic, hypertensive, 55+ years, mean age=66 years].

[g]Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360(9346):1623-1630 [**PROSPER**, Pravastatin in Elderly Individuals at Risk of Vascular Disease: Scotland, Ireland, and Netherlands, men and women, aged 70-82 years].

Table 2.12: Major Primary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality (Cont'd)

[h]Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the ASCOT-LLA: a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158 [**ASCOT-LLA**, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm: United Kingdom, men and women, non-dyslipidemic, hypertensive, aged 40-79 years].

[i]Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the CARDS: multicentre randomised placebo-controlled trial. *Lancet.* 2004;364(9435):685-696 [**CARDS**, Collaborative Atorvastatin Diabetes Study: United Kingdom & Ireland with 132 sites, 5 Nordic countries, men and women, type 2 diabetic, non-hyperlipidemic, aged 40-75 years].

[j]Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet.* 2006;368(9542):1155-1163 [**MEGA**, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese: Japan, 924 sites, men and women, hypercholesterolemic, aged 40-70 years].

[k]Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the ASPEN. *Diabetes Care.* 2006;29(7):1478-1485 [**ASPEN**, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus: 14 countries, 70 centers, men and women, type 2 diabetic, low LDL-C, aged 40-75 years].

[l]Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-2207 [**JUPITER**, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin: 26 countries, 1315 sites, men 50+ years, women 60+ years, high C-reactive protein levels, non-hyperlipidemic).

[m]Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis.* 2005;178(2):387-397 [**HYRIM**, Hypertension High Risk Management: Norway, men and women aged 40-74 years with hypertension].

Table 2.13: The Effect of Treatment with Different Statins on Lipid Profiles				
	% Change in Lipid Profile			
Statin	**↓LDL-C**	**↓TC**	**↑HDL-C**	**↓TG**
Lovastatin	29-48	21-36	7-8	2-13
Pravastatin	20-30	15-22	3-6	8-13
Simvastatin	28-46	20-33	5-7	12-18
Fluvastatin	17-23	13-19	0.9	5-13
Atorvastatin	37-51	27-39	2-6	20-28
Rosuvastatin	46-55	33-40	8-10	20-26
Pitavastatin	39-44	28-32	4-6	14-19

Source: Ewang-Emukowhate M, Wierzbicki AS. Lipid-lowering agents. *J Cardiovasc Pharmacol Ther.* 2013.

Abbreviations: LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; HDL-C, High- density lipoprotein cholesterol; TG, Triglycerides.

Table 2.14: Effects of Different Doses of Lipid-Lowering Agents on Lipid Profiles				
Drug	**Dose/day**	**Effect on LDL-C (%)**	**Effect on HDL-C (%)**	**Effect on TG (%)**
STATINS				
Atorvastatin	10 mg	-39	+6	-19
	20 mg	-43	+9	-26
	40 mg	-50	+6	-29
	80 mg	-60	+5	-37
Fluvastatin	20 mg	-22	+3	-12
	40 mg	-25	+4	-14
	80 mg	-36	+6	-18
Lovastatin	10 mg	-21	+5	-10
	20 mg	-24	+7	-10
	40 mg	-30	+7	-14
	80 mg	-40	+9.5	-19
Pitavastatin	1 mg	-32	+8	-15
	2 mg	-36	+7	-19
	4 mg	-43	+5	-18
Pravastatin	10 mg	-22	+7	-15
	20 mg	-32	+2	-11
	40 mg	-34	+12	-24
	80 mg	-37	+3	-19

Table 2.14: Effects of Different Doses of Lipid-Lowering Agents on Lipid Profiles (Cont'd)				
Drug	**Dose/day**	**Effect on LDL-C (%)**	**Effect on HDL-C (%)**	**Effect on TG (%)**
Rosuvastatin	5 mg	-45	+13	-35
	10 mg	-52	+14	-10
	20 mg	-55	+8	-23
	40 mg	-63	+10	-28
Simvastatin	5 mg	-26	+10	-12
	10 mg	-30	+12	-15
	20 mg	-38	+8	-19
	40 mg	-41	+13	-28
	80 mg	-47	+16	-33
BILE ACID SEQUESTRANTS				
Cholestyramine	4-24 g	-15 to -30	+3 to +5	+0 to +20
Colesevelam	6 tablets	-15	+3	+10
	7 tablets	-18	+3	+9
Colestipol	7-30g	-15 to -30	+3 to +5	+0 to +20
FIBRIC ACID DERIVATIVES				
Fenofibrate	67-200 mg	-20 to -31	+9 to +14	-30 to -50
Gemfibrozil	600 mg twice daily	-5 to -10[a]	+10 to +20	-40 to -60
2-AZETIDINONE				
Ezetimibe	10 mg	-15 to -20	+1 to +4	-5 to -8
OMEGA-3-ACID ETHYL ESTERS				
	4 g	+44.5	+9.1	-44.9
MICROSOMAL TRIGLYCERIDE TRANSPORT PROTEIN (MTP) INHIBITOR				
Lomitapide	5-60 mg	-40	-7	-45

Table 2.14: Effects of Different Doses of Lipid-Lowering Agents on Lipid Profiles (Cont'd)				
Drug	**Dose/day**	**Effect on LDL-C (%)**	**Effect on HDL-C (%)**	**Effect on TG (%)**
COMBINATION PRODUCTS				
Ezetimibe/Simvastatin	10/10 mg	-45	+8	-23
	10/20 mg	-52	+10	-24
	10/40 mg	-55	+6	-23
	10/80 mg	-60	+6	-31
Niacin/Lovastatin	1000/20 mg	-30	+20	-32
	1000/40 mg	-36	+20	-39
	1500/40 mg	-37	+27	-44
	2000/40 mg	-42	+30	-44
Niacin/Simvastatin	1000/20 mg	-12	+21	-27
	1000/40 mg	-7	+15	-23
	2000/20 mg	-14	+29	-38
	2000/40 mg	-5	+24	-32

Source: Hyperlipidemia management. Lexicomp Online; 2013.
Abbreviations: LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; TG, Triglycerides.
[a]May increase LDL in some patients**.**

2.2.8 Efficacy of Statins in Secondary Prevention

People with established CHD are at very high risk for recurrent CVD events.[140] Several notably large secondary prevention statin trials provide strong evidence for the benefit of cholesterol lowering therapy using statins in persons with established CHD.[141] Results from these and other statin trials provide evidence of the efficacy of statins at reducing LDL-C, with an accompanied reduction in cardiovascular morbidity, mortality, and all-cause mortality. LDL-lowering using statins has been shown to produce significant cardiovascular benefit without regard to patients' gender, age, diabetes, smoking, and hypertension status.[142] In patients with CHD, LDL-lowering has been

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[140] "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report."

[141] "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)."; Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001-9; Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Ibid.1998;339(19):1349-57; "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)."; "MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial."; Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin. 2002;18(4):220-8; LaRosa JC et al., "Intensive lipid lowering with atorvastatin in patients with stable coronary disease."; Pedersen TR et al., "High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial."; Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549-59; Search Study Collaborative Group, Bowman L, Armitage J, Bulbulia R, Parish S, and Collins R. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. Am Heart J. 2007;154(5):815-23; Kjekshus J et al., "Rosuvastatin in older patients with systolic heart failure."

[142] Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, and Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care. 1997;20(4):614-20; Goldberg

shown to cause a reduction in the relative risk of stroke,[143] improvement of angina and myocardial perfusion,[144] and decrease in the need for subsequent coronary revascularization.[145]

RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. Circulation. 1998;98(23):2513-9; Sacks FM et al., "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators."; Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation. 1995;92(9):2419-25; Waters D, Higginson L, Gladstone P, Boccuzzi SJ, Cook T, and Lesperance J. Effects of cholesterol lowering on the progression of coronary atherosclerosis in women. A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) substudy. Ibid.:2404-10; Kjekshus J, and Pedersen TR. Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol. 1995;76(9):64C-68C; Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation. 1997;96(12):4211-8.

143 "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."; "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)."; Sacks FM et al., "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators."; Crouse JR, Byington RP, Hoen HM, and Furberg CD. Reductase inhibitor monotherapy and stroke prevention. Arch Intern Med. 1997;157(12):1305-10; Hebert PR, Gaziano JM, Chan KS, and Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA. 1997;278(4):313-21.

144 Kjekshus J and Pedersen TR, "Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S)."; Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, and Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med. 1995;332(8):488-93; Aengevaeren WR, Uijen GJ, Jukema JW, Bruschke AV, and van der Werf T. Functional evaluation of lipid-lowering therapy by pravastatin in the Regression Growth Evaluation Statin Study (REGRESS). Circulation. 1997;96(2):429-35; Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). Am J Cardiol. 1998;81(3):333-5; Gould AL, Rossouw JE, Santanello NC, Heyse JF, and Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation. 1998;97(10):946-52.

145 "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."; The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. The Post Coronary Artery Bypass Graft Trial Investigators. N Engl J Med. 1997;336(3):153-62; "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)."; Sacks FM et al., "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators."; Knatterud GL, Rosenberg Y, Campeau L, et al. Long-term effects on clinical outcomes of

Table 2.15 provides a summary of the results of major secondary prevention trials of statins.

aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. Post CABG Investigators. Circulation. 2000;102(2):157-65.

Table 2.15: Major Secondary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality										
Trials	**Dates**	**Follow-up (years)**	**Sample Size**	**Treatment Dose/day**	**Control**	**Baseline LDL-C (mg/dL)[a]**	**LDL-C Change (%)[b]**	**Major Coronary Events (%)[c]**	**Coronary Mortality (%)**	**All-cause Mortality (%)**
4S[d]	1988-1994	5.4	4,444	Simvastatin 20-40mg	Placebo	188	-35*	-34*	-42*	-30*
CARE[e]	1989-1996	5.0	4,159	Pravastatin 40mg	Placebo	139	-30*	-25*	-24*	NS
LIPID[f]	1990-1997	6.1	9,014	Pravastatin 40mg	Placebo	150	-25*	-29*	-24*	-22*
GISSI-P[g]	1993-1996	1.9	4,271	Pravastatin 20mg	Usual care	152	-15*	NS	-40*	NS
HPS[h]	1994-2001	5.0	20,536	Simvastatin 40mg	Placebo	131	-41*	-26*	-17*	-12*
GREACE[i]	1998-2001	3.0	1,600	Atorvastatin 10-80mg	Usual care	179	-46*	-51*	-42*	-42*
LIPS[j]	1998-2002	3.8	1,677	Fluvastatin 40mg	Placebo	131	-26*	NS	NS	NS
TNT[k]	1998-2005	4.9	10,001	Atorvastatin 80mg	Atorvastatin 10mg	152	-49*	-20*	-20*	NS
SPARCL[l]	1998-2005	4.9	4,731	Atorvastatin 80mg	Placebo	133	-45*	NS	NS	NS
SEARCH[m]	1998-2008	6.7	12,064	Simvastatin 80mg	Simvastatin 20mg	97	-11*	NS	NS	NS
IDEAL[n]	1999-2005	4.8	8,888	Atorvastatin 80mg	Simvastatin 20-40mg	122	-34*	-18*	NS	NS

Table 2.15: Major Secondary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality (Cont'd)										
CORONA[o]	2003-2007	2.8	5001	Rosuvastatin 10mg	Placebo	137	-45*	NS	NS	NS
JAPAN-ACS[p]	2005-2007	1.0	307	Pitavastatin 4mg	Atorvastatin 20mg	131	-20*	NS	NA	NA

Source: Kizer JR, Madias C, Wilner B, et al. Relation of different measures of low-density lipoprotein cholesterol to risk of coronary artery disease and death in a meta-regression analysis of large-scale trials of statin therapy. *Am J Cardiol.* 2010;105(9):1289-1296; Published articles for each trial results; and TrialResultsCenter.org.

Abbreviations: LDL-C, Low-density lipoprotein cholesterol; NS, Not statistically significant; NA, Not applicable.

*Relative risk reduction is statistically significant at $p<0.05$.

[a]Mean baseline LDL-C for the whole group.

[b]LDL-C percentage change from baseline to follow-up for treatment only.

[c]Major coronary events include fatal and non-fatal myocardial infarction or stroke, coronary revascularization, coronary artery bypass surgery, and unstable angina.

[d]Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the 4S Group. *Lancet.* 1994;344(8934):1383-1389 [**4S**, Scandinavian Simvastatin Survival Study: 5 Nordic countries, 94 sites, men and women aged 35-69 years, history of angina pectoris and MI, myocardial infarction].

[e]Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels (CARE Trial investigators). *N Engl J Med.* 1996;335(14):1001-1009 [**CARE**, Cholesterol and Recurrent Events trial: US and Canada, 80 centers, men and women aged 21-75 years, history of acute MI].

[f]Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels (LIPID Study Group). *N Engl J Med.* 1998;339(19):1349-1357 [**LIPID**, Long-Term Intervention with Pravastatin in Ischaemic Disease: Australia and New-Zealand, 87 centers, men and women aged 31-75 years, history of MI and unstable angina].

[g]Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI-P Investigators. *Ital Heart J.* 2000;1(12):810-820 [**GISSI-P**, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione: Italy, men and women with history of acute MI].

Table 2.15: Major Secondary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality (Cont'd)

[i]Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention (The GREACE study). *Curr Med Res Opin.* 2002;18(4):220-228 [**GREACE**, GREek Atorvastatin and Coronary-heart-disease Evaluation: Greece, men and women, mean age of 59 years, history of MI or CHD].

[j]Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;287(24):3215-3222 [**LIPS**, Lescol Intervention Prevention Study: Europe, Canada and Brazil, 77 centers, men and women aged 18-80 years, history of angina and silent ischemia with first percutaneous coronary intervention].

[k]LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352(14):1425-1435 [**TNT**, Treating to New Targets clinical trial: 14 countries, 256 centers, men and women aged 35-75 years, history of chronic coronary artery disease, CAD].

[l]Amarenco P, Bogousslavsky J, Callahan A, III, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355(6):549-559 [**SPARCL**, Stroke Prevention by Aggressive Reduction in Cholesterol Levels: 25 countries, 130 locations, men and women aged 18 years and older, history of stroke or transient ischemia].

[m]Search Study Collaborative Group, Bowman L, Armitage J, Bulbulia R, Parish S, Collins R. SEARCH: characteristics of a randomized trial among 12064 myocardial infarction survivors. *Am Heart J.* 2007;154(5):815-823 [**SEARCH**, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine: UK, 88 centers, men and women aged 18-80 years, history of MI].

[n]Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005;294(19):2437-2445 [**IDEAL**, Incremental Decrease in End Points Through Aggressive Lipid Lowering: 5 Nordic countries, 190 centers, men and women aged 18-80 years, history of MI].

[o]Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357(22):2248-2261 [**CORONA**, Controlled Rosuvastatin Multinational Study in Heart Failure: 21 countries, 378 centers, men and women aged 60 years and older, history of systolic heart failure].

Table 2.15: Major Secondary Prevention Statin Trials and Effects on LDL-C and Cardiovascular Morbidity and Mortality (Cont'd)
[p]Hiro T, Kimura T, Morimoto T, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS study). *J Am Coll Cardiol.* 2009;54(4):293-302 [**JAPAN-ACS**, Japan Assessment of Pitavastatin and Atorvastatin In Acute Coronary Syndrome: Japan, 33 centers, men and women aged 20 years and older, history of acute coronary syndrome].

2.2.9 Efficacy of Statin Dosage Intensity in Primary and Secondary Prevention

The intensity of statin dosing is believed to have a direct relationship with the magnitude of the lipid modifying and cardiovascular benefit of statins.[146] Overall, evidence from RCTs indicates that high-intensity statins reduce ASCVD risk more than moderate-intensity or low-intensity statins in primary and secondary prevention of cardiovascular disease.[147] For example, the Treating to New Target (TNT) trial comparing the efficacy of daily doses of atorvastatin 80mg and 10mg showed significant reductions in LDL-C, major coronary events, and coronary mortality in the atorvastatin 80mg group compared to the atorvastatin 10mg group.[148] However, the effectiveness of intensive statin dosing is more correlated with LDL-C reduction than with improvement of cardiovascular outcomes as found in other trials.[149]

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[146] Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152-60; Jones P, Kafonek S, Laurora I, and Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). Ibid.1998;81(5):582-7; Betteridge J. Pitavastatin - results from phase III & IV. Atheroscler Suppl. 2010;11(3):8-14.

[147] Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

[148] LaRosa JC et al., "Intensive lipid lowering with atorvastatin in patients with stable coronary disease."; ibid.

[149] Armitage J et al., "Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial."; Pedersen TR et al., "High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial."

2.2.10 Statin Dosage and Administration

Several primary and secondary prevention statin trials have demonstrated scientific evidence for usage of statins in various disease conditions. Statins often achieve clinical efficacy at different doses, with higher doses achieving greater LDL-C reduction but with greater possibility of side effects. The Table 2.16 provides a summary of the dosage and administration schedule of currently available statins and statin combination products, while Table 2.17 provides a summary of dosage equivalents for statins.

Table 2.16: Statin Dosage and Administration						
Statin	**US Brand Names**	**FDA-Approved Indications[a]**	**Starting Dose (mg/day)[b,c]**	**Maximum Dose (mg/day)[b,c]**	**Available Strength (mg)**	**Administration Considerations[d,e,f]**
Lovastatin	Mevacor® Altoprev®	-Primary and secondary prevention of CAD -Primary hypercholesterolemia -Heterozygous familial hypercholesterolemia in pediatric patients (10-17 years)	20 20-60 (ER)	80 60 (ER)	10, 20, 40 (generic) 20, 40 (Mevacor®) 20,40, 60 (ER-Altoprev®)	-Administer immediate release tablet with the evening meal -Administer extended release tablet at bedtime; do not crush or chew.
Pravastatin	Pravachol®	-Primary and secondary prevention of CAD. -Primary hypercholesterolemia -Heterozygous familial hypercholesterolemia in pediatric patients (8-18 years)	10-80	80	10, 20, 40, 80 (generic) 20, 40, 80 (Pravachol®)	-May be taken without regard to meals

Table 2.16: Statin Dosage and Administration (Cont'd)						
Statin	**US Brand Names**	**FDA-Approved Indications[a]**	**Starting Dose (mg/day)[b,c]**	**Maximum Dose (mg/day)[b,c]**	**Available Strength (mg)**	**Administration Considerations[d,e,f]**
Simvastatin	Zocor®	-Secondary prevention of CHD to reduce morbidity, mortality and stroke -Primary hypercholesterolemia -Homozygous familial hypercholesterolemia -Heterozygous familial hypercholesterolemia	5-40	80[g]	5, 10, 20, 40, 80 (generic and Zocor®)	-May be taken without regard to meals -Better taken in the evening
Fluvastatin	Lescol® Lescol-XL®	-Primary and secondary prevention of CAD -Primary hypercholesterolemia (heterozygous familial and non-familial) -Mixed dyslipidemia -Heterozygous familial hypercholesterolemia in pediatric patients (10-16 years) -Diabetic dyslipidemia	20	80 (XL) 40mg bid	20, 40 (generic and Lescol®) 80 (Lescol-XL®)	-May be taken without regard to meals (food reduces rate but not the extent of absorption) -Should be given 2 hours after a bile-acid sequestrants or niacin -Do not break, chew, or crush extended release tablets; do not open capsules

Table 2.16: Statin Dosage and Administration (Cont'd)						
Statin	**US Brand Names**	**FDA-Approved Indications[a]**	**Starting Dose (mg/day)[b,c]**	**Maximum Dose (mg/day)[b,c]**	**Available Strength (mg)**	**Administration Considerations[d,e,f]**
Atorvastatin	Lipitor®	-Primary and secondary prevention of CAD -Primary hypercholesterolemia (heterozygous familial and non-familial) -Heterozygous familial hypercholesterolemia in pediatric patients (10-17 years)	10-80	80	10, 20, 40, 80 (generic and Lipitor®)	May be taken without regard to meals at any time of day
Rosuvastatin	Crestor®	-Primary and secondary prevention of CAD -Primary hypercholesterolemia -Increase HDL-C -Primary dysbetalipoproteinemia -Homozygous familial hypercholesterolemia -Heterozygous familial hypercholesterolemia in pediatric patients (10-17 years)	5-40	40	5, 10, 20, 40 (Crestor®)	May be taken without regard to meals at any time of day

Table 2.16: Statin Dosage and Administration (Cont'd)						
Drug/ Statin	**US Brand Names**	**FDA-Approved Indications[a]**	**Starting Dose (mg/mg per day)[b,c]**	**Maximum Dose (mg/mg per day)[b,c]**	**Available Strength (mg/mg)**	**Administration Considerations[d,e,f]**
Pitavastatin	Livalo®	-Primary hyperlipidemia -Mixed dyslipidemia	2	4	1, 2, 4 (Livalo®)	May be administered with or without food and taken without regard to time of day
Statin Combination Formulations						
Niacin/ Lovastatin	Advicor®	(See lovastatin)	500/20	2000/40	500/20, 750/20, 1000/20, 1000/40 (Advicor®)[h]	Should be taken at bedtime with a low-fat snack; Swallowed whole; do not crush or chew
Ezetimibe/ Simvastatin	Vytorin®	(See simvastatin)	10/10-40	10/80[g]	10/10, 10/20, 10/40, 10/80 (Vytorin®)	(See simvastatin) Should be taken ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant
Niacin/ Simvastatin	Simcor®	(See simvastatin)	500/20-40	2000/40	500/20, 500/40, 750/20, 1000/20, 1000/40 (Simcor®)[h]	(See Niacin/Lovastatin)

Table 2.16: Statin Dosage and Administration (Cont'd)						
Drug/ Statin	**US Brand Names**	**FDA-Approved Indications[a]**	**Starting Dose (mg/mg per day)[b,c]**	**Maximum Dose (mg/mg per day)[b,c]**	**Available Strength (mg/mg)**	**Administration Considerations[d,e,f]**
Statin Combination Formulations (Cont'd)						
Sitagliptin/ Simvastatin	Juvisync®	(See simvastatin) -Type 2 diabetes	100/40	NA	50/10, 50/20, 50/40, 100/10, 100/20, 100/40 (Juvisync®)	(See simvastatin) Administer in the evening. Do not split or divide tablet
Amlodipine/ Atorvastatin	Caduet®	(See atorvastatin) -Hypertension -Chronic stable angina -Prinzmetal's angina	5-10/10-80	10/80	2.5/10, 2.5/20, 2.5/40, 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, 10/80 (generic and Caduet®)	(See atorvastatin)
Ezetimibe/ Atorvastatin	Liptruzet®	(See atorvastatin)	10/10-80	10/80	10/10, 10/20, 10/40, 10/80 (Liptruzet®)	(See atorvastatin) Administer ≥2 hours before or ≥4 hours after bile acid sequestrants

Source: Lexicomp Online, 2013. US Food and Drug Administration. National Drug Code query-active ingredient, 2013.
Abbreviations: FDA, US Food and Drug Administration; LDL-C, Low-density lipoprotein cholesterol; XL or ER, Extended release tablet or capsule; CAD, Coronary artery disease; CHD, Coronary heart disease; NA, Information is not available.
[a]Use in indications is to reduce blood levels of total cholesterol, LDL-C, apolipoprotein B, and triglyceride.
[b]Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and patient response; adjustments should be made at intervals of 4 weeks or more.

Table 2.16: Statin Dosage and Administration (Cont'd)

[c]All adult dosing information; dosage forms are immediate release unless otherwise stated.
[d]Avoid large quantities of grapefruit juice (>1 quart/day) and red yeast rice (contains an estimated 2.4 mg lovastatin per 600 mg rice).
[e]Consumption of large amounts of ethanol may increase the risk of liver damage with statins.
[f]St. John's wort may decrease the bioavailability of statins; avoid.
[g]If patient is unable to achieve LDL-C goal using the 40 mg dose of simvastatin, increasing to 80 mg dose is not recommended. Instead, switch patient to an alternative LDL-C-lowering treatment providing greater LDL-C reduction.
[h]All niacin doses are in extended release form.

Table 2.17: Statin Dosage Equivalency in Patients with Hypercholesterolemia*

Dose Level	Fluvastatin (mg)	Pravastatin (mg)	Lovastatin (mg)	Pitavastatin (mg)	Simvastatin (mg)	Atorvastatin (mg)	Rosuvastatin (mg)	% LDL-C Reduction
1	20	10	10					15-20
2	40	20	20		5-10			21-29
3	80-XL	40-80	40	1-2	20	10		30-38
4			80	4	40	20	5-10	39-47
5					80	40	20	48-54
6						80	40	55-59

Source: Texas Diabetes Council. Lipid algorithm for type 1 and type 2 diabetes mellitus in adults; 2011.
*Information not completely based on head to head comparison.

2.2.11 Complications, Contraindications, and Adverse Effects

Statins are generally well tolerated and are believed to have minimal adverse effects.[150] However, statin-associated adverse events including elevations of liver enzymes, myopathies, and rhabdomyolysis demands special monitoring and clinical considerations.[151] Discontinuation and/or reduction of the statin dose usually lead to resolution of these side effects.[152] Recently, however, debate has focused on the possible, negative long-term effects of statin treatment on cognitive decline,[153] colorectal cancer risk,[154] and diabetes mellitus.[155]

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[150] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, and Lenfant C. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. Stroke. 2002;33(9):2337-41.

[151] Ibid.

[152] Bruckert E, Hayem G, Dejager S, Yau C, and Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther. 2005;19(6):403-14.

[153] Beydoun MA, Beason-Held LL, Kitner-Triolo MH, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. J Epidemiol Community Health. 2011;65(11):949-57; Rojas-Fernandez CH, and Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother. 2012;46(4):549-57.

[154] Lakha F, Theodoratou E, Farrington SM, et al. Statin use and association with colorectal cancer survival and risk: case control study with prescription data linkage. BMC Cancer. 2012;12(1):487.

[155] Coleman CI et al., "The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials."; Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."; Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."; Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."; Athyros VG, and Mikhailidis DP. Pharmacotherapy: statins and new-onset diabetes mellitus--a matter for debate. Nat Rev Endocrinol. 2012;8(3):133-4; Colbert JD, and Stone JA. Statin use and the risk of incident diabetes mellitus: a review of the literature. Can J Cardiol. 2012;28(5):581-9; Jukema JW, Cannon CP, de Craen AJ, Westendorp RG, and Trompet S. The controversies of statin therapy: weighing the evidence. J Am Coll Cardiol. 2012;60(10):875-81; Kaski JC. High dose statin treatment and new onset diabetes. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy. 2011;25(6):571-72; Katsiki N, and Banach M. Statin use and risk of diabetes mellitus in postmenopausal women. Clin Lipidol. 2012;7(3):267; Luca M, and Mark RG. Long-standing statin therapy and the risk of new-onset diabetes in the elderly. Drugs Aging. 2012;29(1):9-13; Mizuno K, Tajima N, Ohashi Y, and Nakamura H. Is the risk of new-onset diabetes by statins associated with diet adherence? Int J Cardiol. 2012; Preiss D, and Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol. 2011;22(6):460-6; Preiss D, and Sattar N. Pharmacotherapy: Statins and new-onset diabetes--

Muscle Toxicity and Elevation of Liver Enzymes

Despite their cardiovascular benefit in primary and secondary prevention of CVD, statins as a therapeutic class are associated with clinically significant muscle problems that include: (1) myopathy (i.e., a general term referring to any disease of muscles); (2) myalgia (i.e., muscle ache or weakness without creatine kinase elevation); (3) myositis (i.e., muscle symptoms with increased creatine kinase levels); and (4) rhabdomyolysis (i.e., muscle symptoms with marked creatine kinase elevation that is substantially greater than 10 times the upper limit of normal, and with creatinine elevation that is accompanied by brown urine and urinary myoglobin).[156] Cerivastatin (Baycol® and Lipobay®) was withdrawn from the US market on August 8, 2001 as a result of severe incidences of rhabdomyolysis.[157]

Several conditions increase the risk of statin-induced myopathy. These include patient-related factors and factors related to drug interactions. Patient-related risk factors include advanced age – especially for people 80 years of age or greater, female gender, having a low body mass index, strenuous exercise, surgery requiring high metabolic demands, and disease conditions such as impaired renal or liver function, hypothyroidism, diabetes mellitus, biliary tract obstruction, and inflammatory or inherited

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the important questions. Nat Rev Cardiol. 2012;9(4):190-2; Sattar N, and Taskinen MR. Statins are diabetogenic--myth or reality? Atheroscler Suppl. 2012;13(1):1-10.

[156] Pasternak RC et al., "ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins."

[157] U.S. Food and Drug Administration, "Safety: Baycol (cerivastatin sodium tablets) Aug 2001".

metabolic muscle defects (e.g., McArdle's disease and carnitine palmityl transferase II deficiency).[158]

The risk of myopathy also is increased with heavy alcohol consumption and in drug abuse (e.g., cocaine, amphetamines, and heroin); and when statins are co-administered with grapefruit juice (greater than 1 quart per day), other lipid-lowering drugs (especially gemfibrozil, fibrates, and niacin), and drugs metabolized through the cytochrome P-450 3A4 enzyme system: macrolide antibiotics (e.g., azithromycin and erythromycin), antifungals (e.g., fluconazole and ketoconazole), protease inhibitors (e.g., amprenavir and indinavir), nefazodone, amiodarone, calcium antagonists (e.g., verapamil and diltiazem), and warfarin.[159]

Despite the clinical seriousness of statin-induced myopathies, lower incidences of myopathies appeared to have been reported by RCTs of statins compared to reports from observational studies. For example, major statin trials such as the Heart Protection Study (HPS), WOSCOPS and the Scandinavian Simvastatin Survival Study (4S) have reported myopathy incidences of 0.11%, 0.12%, and 0.27%, respectively.[160] In contrast, higher incidences of statin-induced myopathy, ranging from 5-10%, have been reported in

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[158] Rallidis LS, Fountoulaki K, and Anastasiou-Nana M. Managing the underestimated risk of statin-associated myopathy. Int J Cardiol. 2012;159(3):169-76.

[159] Ibid.

[160] Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."; "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)."; "MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial."

observational studies.[161] The lower incidences of myopathies reported in RCTs might be due to strict criteria required for trial participation, such as the initial exclusion, from statin trials, of patients with increased risk factors for myopathy (e.g., patients with histories of muscle symptoms, creatine kinase (CK) elevations, and renal or liver diseases).[162] Nevertheless, recent evidence from a meta-analysis of 246,955 participants from 135 RCTs which evaluated the comparative tolerability and harms of statins in subjects with and without CVD indicated that statins users were not different than controls in terms of myalgia, CK elevation, and discontinuation of therapy due to adverse events.[163] Another meta-analysis of 35 randomized statin trials has confirmed similar observation.[164]

The most common clinical symptoms of myopathy ranges from mild muscle fatigue and pains to symptoms such as diffuse muscle pains, weakness, low back pain, proximal muscle pain and aching, or the flu-like symptom manifestation of rhabdomyolysis – the rarest form of myopathy requiring hospitalization of the patient.[165] However, reported incidence of rhabdomyolysis is low (~3.2/100,000 person years), with

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[161] Nichols GA, and Koro CE. Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. Clin Ther. 2007;29(8):1761-70; Bruckert E et al., "Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study."

[162] Rallidis LS et al., "Managing the underestimated risk of statin-associated myopathy."

[163] Naci H et al., "Comparative tolerability and harms of individual statins: A study-level network meta-analysis of 246 955 participants from 135 randomized controlled trials."

[164] Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006;114(25):2788-97.

[165] Antons KA, Williams CD, Baker SK, and Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. Am J Med. 2006;119(5):400-9.

incidence having the potential to increase by almost 12 times when statins are combined with gemfibrozil.[166]

Mechanism

The mechanism of statin-induced myopathy is unclear, but has been attributed to instability of cell membranes caused by a decreased cholesterol synthesis and/or decreased ubiquinone (Coenzyme Q_{10} or CoQ_{10}) production, a process considered essential for mitochondrial electron transport.[167] CoQ_{10} supplementation is believed to mitigate myopathy-related complaints, but there is insufficient evidence to support its usefulness in alleviating statin-induced myopathies.[168]

Management

Myopathies and rhabdomyolysis are serious statin adverse effects warranting an immediate discontinuation of the statin therapy or a significant reduction of the statin dose.[169] Because several factors could cause an increased serum CK levels, routine measurement of CK is considered not helpful in detecting rare cases of statin-induced myopathy; instead, CK levels are recommended to be measured upon a patient's report of unexplained or new muscle pain, tenderness, or weakness, or the evidence of a brown urine. When the level of serum CK are greater than 10,000 Units/L, patients should be

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[166] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292(21):2585-90; Black C, and Jick H. Etiology and frequency of rhabdomyolysis. Pharmacotherapy. 2002;22(12):1524-6.

[167] Chapman MJ, and Carrie A. Mechanisms of statin-induced myopathy: a role for the ubiquitin-proteasome pathway? Arterioscler Thromb Vasc Biol. 2005;25(12):2441-4.

[168] Marcoff L, and Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. J Am Coll Cardiol. 2007;49(23):2231-7.

[169] Bruckert E et al., "Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study."

placed on high fluid intake to avoid azotemia and kidney damage. Upon continued evaluation and treatment, the muscle pain and high CK levels may dissipate within a few days, with full recovery expected within a week. Because of the possibility of drug interaction-induced myopathies, a review of the patient's medication list is necessary to remove the offending drug before statin therapy is re-instated. Re-introduction of the statin therapy should be done at a lower dose, or by switching to an alternate statin with better adverse effect profile.[170]

[170] Baliga RR, *Statin prescribing guide*.

2.3 SECTION III: DIABETES MELLITUS

2.3.1 Introduction

Diabetes mellitus is a group of metabolic diseases in which there is increased level of blood sugar (hyperglycemia) which results from defects in insulin secretion, insulin action, or both.[171] Hyperglycemia is defined as serum glucose level > 180 mg/dL that persists for more than 2 hours.[172] The two major forms of diabetes mellitus occur because of an absolute lack of insulin production which is a result of an auto-immune destruction of the insulin-producing pancreatic β-cells (type 1 diabetes), or because individuals are not able to efficiently use the normal insulin secreted by their pancreatic β-cells (type 2 diabetes).[173] Either form of diabetes results in high blood sugar levels (hyperglycemia), which produces the classical symptoms of frequent urination (polyuria), increased thirst (polydipsia), and increased hunger (polyphagia).[174] Diabetes mellitus is a chronic illness requiring constant medical care that includes patient self-management, education, and support to prevent acute complications such as hypoglycemia, and to reduce the risk of long-term complications such as retinopathy and diabetic neuropathy.[175]

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[171] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81-90.
[172] Rehman A, Setter SM, and Vue MH. Drug-induced glucose alterations part 2: Drug-induced hyperglycemia. Diabetes Spectrum. 2011;24(4):234-38.
[173] Kagan A. Type 2 diabetes : social and scientific origins, medical complications and implications for patients and others. Vol. ed. Jefferson, NC: McFarland & Company, Inc; 2010.
[174] Shoback D, and Gardner DG. Greenspan's Basic & Clinical Endocrinology. Vol. 9th ed. New York, NY: McGraw-Hill Medical; 2011.
[175] American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.

2.3.2 Epidemiology

Almost 350 million people are affected by diabetes worldwide, with increasing prevalence in the United States.[176] According to the 2009 – 2012 National Health and Nutrition Examination Survey estimates applied to 2012 US Census data, the Centers for Disease Control and Prevention (CDC) reported that 28.9 million (12.3%) Americans aged 20 years and older have diagnosed diabetes, while another 86 million (37%) have prediabetes – a preclinical condition associated with increased risk of diabetes, heart disease and stroke.[177] These 2014 National Diabetes Statistics Report has since surpassed those released in 2010 which puts the numbers of diagnosed diabetes and prediabetes among Americans aged 20 years and older at 25.6 million (11.3%) and 79 million (35%), respectively.[178] The report indicates that diabetes prevalence has increased since 2010, but incidence has decreased slightly from 1.9 million people who were newly diagnosed with diabetes in 2010,[179] to 1.7 million in 2012.[180] A CDC estimate of data from the National Health Interview Survey (NHIS) put the age-adjusted incidence of diabetes among Americans at 7.6 per 1000 population.[181]

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[176] Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet. 2011;378(9785):31-40.

[177] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."

[178] Centers for Disease Control and Prevention, "National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States."

[179] Ibid.

[180] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."

[181] Centers for Disease Control and Prevention (CDC). Crude and age-adjusted incidence of diagnosed diabetes per 1,000 population aged 18–79 years, United States, 1980–2011. 2012; Available at: http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm. Accessed 12/06, 2012.

As mentioned above, the percentage of the population with diagnosed diabetes continues to rise, with one study projecting that as many as a third of US adults could have diabetes by 2050 if the current trends continue.[182] What makes diabetes a particularly more frightening pandemic is that nearly 28 percent of those with diabetes (approximately 8 million Americans) are unaware of their disease.[183] This makes unmanaged diabetes a major killer disease that is accompanied by serious complications such as kidney failure, cardiovascular diseases, amputations, and blindness – conditions contributing significantly to the overall health care cost of the nation.[184]

2.3.3 Economic Burden

Diabetes imposes a substantial burden on the US economy in the forms of increasing direct medical cost of diabetes treatment, and in indirect medical cost due to lost productivity from work-related absenteeism, chronic disability and premature mortality.[185] The society also pays a high intangible cost in the form of reduced quality of life, and pain and suffering of the patients, their families, and friends.[186]

Diabetes-associated treatment cost has increased by 41% since 2007, from $174 billion to an estimated $245 billion in 2012, accounting for a large portion of the total US

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[182] Boyle JP, Thompson TJ, Gregg EW, Barker LE, and Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010;8:29.
[183] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."
[184] Centers for Disease Control and Prevention, "National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States."; American Diabetes Association, "Economic costs of diabetes in the U.S. in 2012."
[185] American Diabetes Association, "Economic costs of diabetes in the U.S. in 2012."
[186] Ibid.

healthcare cost.[187] Even though people with diabetes comprise less than 10% of the total US population,[188] expenditures associated with diabetes accounts for more than 20% of the total health care cost, with diabetics incurring an average medical expenditure of approximately $13,700 annually. This expenditure is approximately 2.3 times higher than what would have been in the absence of diabetes.[189]

Diabetes is the seventh leading cause of death in the US, with risk of mortality doubling for people with diabetes compared to people of similar age without diabetes. Diabetics, compared to people without diabetes, are also at increased risk of suffering from complications such as heart attacks, stroke, high blood pressure, kidney failure, blindness and amputations of feet and legs.[190] The combined cost of hospital inpatient care and prescription medications to treat these complications alone stands at almost $150 billion in 2012.[191] Therefore, a better understanding of the economic and social cost of diabetes should be a major motivation to reduce its prevalence and burden.

2.3.4 Classification

According to the American Diabetes Association, diabetes can be classified into four major categories. These include type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes resulting from other causes.[192]

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[187] Ibid.
[188] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."
[189] American Diabetes Association, "Economic costs of diabetes in the U.S. in 2012."
[190] Centers for Disease Control and Prevention, "National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States."
[191] American Diabetes Association, "Economic costs of diabetes in the U.S. in 2012."
[192] American Diabetes Association, "Standards of medical care in diabetes--2014."

Type 1 diabetes (also known as insulin dependent diabetes or juvenile diabetes) results from an auto-immune destruction of the insulin-secreting pancreatic β-cells, leading to absolute insulin deficiency.[193] It is a metabolic disorder affecting about 5 to 10 percent of people who are diabetic, with diagnoses often occurring before the age of thirty.[194]

People with type 2 diabetes (also known as non-insulin dependent diabetes or adult-onset diabetes) have a relative insulin deficiency in spite of their relatively functioning pancreatic β-cells. The deficiency is due to a combination of metabolic processes that includes peripheral tissue insulin resistance, defective insulin secretion, and increased hepatic glucose output.[195] Type 2 diabetes is a genetically mediated metabolic disease in which the majority of cases is associated with unhealthy lifestyle, often progressing to insulin dependence after eight to ten years of onset.[196] Approximately 90 to 95 percent of people with diabetes have type 2 diabetes.[197]

Gestational diabetes is discovered during pregnancy. It is usually not considered overt diabetes because it is transitory, with blood sugar often returning to normal levels postpartum. This condition is more prevalent among African Americans, Hispanic

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[193] Ibid.
[194] Ali N. Diabetes and you: A comprehensive, holistic approach. Vol. ed. Plymouth, UK: Rowman & Littlefield Publishers, Inc.; 2011.
[195] Seggelke S, and Everhart B. Management of type 2 diabetes. Nurse Pract. 2013;38(6):13-6.
[196] Kagan A, *Type 2 diabetes : social and scientific origins, medical complications and implications for patients and others*.
[197] Ali N, *Diabetes and you: A comprehensive, holistic approach*.

Americans, American Indians, and among women with obesity and family history of diabetes.[198]

Other types of diabetes are identified by other specific causes. These causes include genetic defects of pancreatic β-cells and insulin functions, diseases (e.g., cystic fibrosis), drug or chemical associated with HIV/AIDS treatment, or diabetes associated with after-effects of organ transplantation.[199]

2.3.5 Etiology

Environmental and genetic factors play significant roles in the etiology of both type 1 and type 2 diabetes mellitus.[200] Genetic influence explains why the risk of developing type 1 diabetes in a person increases by 10-20 times those of the general population if that person's immediate relative (i.e., parent, brother, sister, son or daughter) has type 1 diabetes.[201] Similarly, the likelihood of someone having type 2 diabetes is three times the risk for the general population if one of the parents has type 2 diabetes. This risk increases to fourfold if both parents have the disease.[202]

The influence of environmental factors in the etiology of type 1 diabetes explains why the probability that one member of a monozygotic (genetically identical) twin will

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198 Centers for Disease Control and Prevention, "National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States."
199 American Diabetes Association, "Standards of medical care in diabetes--2014."
200 Stankov K, Benc D, and Draskovic D. Genetic and epigenetic factors in etiology of diabetes mellitus type 1. Pediatrics. 2013;132(6):1112-22.
201 Joslin Diabetes Center. Genetics & diabetes : what's your risk? 2014; Available at: http://www.joslin.org/info/genetics_and_diabetes.html. Accessed June 23, 2014.
202 Ibid.

have type 1 diabetes is less than 40% if the other member of the twin has the disease.[203] The increased incidence of type 1 diabetes among population groups that moved from a low to a high incidence region further supports the influence of environmental factors in the etiology of type 1 diabetes.[204]

The epidemic of type 2 diabetes mellitus among Americans has been attributed to increasing rates of environmental factors such as overweight, obesity, inadequate physical activity, and sedentary lifestyle.[205] Because obesity increases insulin resistance, overweight and obese individuals are therefore especially at greater risk for type 2 diabetes.[206]

Moreover, genetic factors may explain why individuals with identical environmental risk exposure may or may not develop diabetes.[207] This epidemiological observation is exemplified by variance in the prevalence of diabetes among diverse ethnic groups sharing a common environment. For example, the Pima Indians of Arizona have the highest reported prevalence of diabetes (40%) of any population in the world.[208] This

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[203] Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, and Akerblom HK. Environmental triggers and determinants of type 1 diabetes. Diabetes. 2005;54 Suppl 2:S125-36.
[204] Ibid.
[205] Kirkman MS et al., "Diabetes in older adults."; Lawrence JM et al., "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005."
[206] Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. Am J Prev Med. 2005;28(1):126-39.
[207] Barnett A. Type 2 diabetes. Vol. 2 ed. Oxford: Oxford University Press; 2012.
[208] Ibid.

is despite sharing a similar unhealthy, high-caloric diet and sedentary lifestyles with the wider US population who has a prevalence of diabetes of 9.3 percent.[209]

2.3.5.1 Drug-induced Diabetes Mellitus

Apart from the influence of genetics and environmental factors, many therapeutic agents can precipitate new onset diabetes especially when pre-existing risk factors are also present. The impairment of glucose metabolism and deterioration of glucose control is also especially pronounced when diabetogenic drugs are taken by those with existing diabetes. Diabetogenic medications act mainly by either increasing insulin resistance, or by inhibiting insulin secretion. Widely used drug therapeutic classes that are considered moderately diabetogenic include thiazide diuretics,[210] β-blockers,[211] antipsychotic agents,[212] antidepressants,[213] and statins. Other drugs, used for special indications, and which are considered more strongly diabetogenic include glucocorticoids (especially

[209] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."

[210] Zillich AJ, Garg J, Basu S, Bakris GL, and Carter BL. Thiazide diuretics, potassium, and the development of diabetes: A quantitative review. Hypertension. 2006;48(2):219-24; Elliott WJ, and Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007;369(9557):201-7.

[211] Kuti EL, Baker WL, and White CM. The development of new-onset type 2 diabetes associated with choosing a calcium channel blocker compared to a diuretic or beta-blocker. Curr Med Res Opin. 2007;23(6):1239-44; Bangalore S, Parkar S, Grossman E, and Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. Am J Cardiol. 2007;100(8):1254-62.

[212] Holt RI, and Peveler RC. Association between antipsychotic drugs and diabetes. Diabetes Obes Metab. 2006;8(2):125-35.

[213] Khoza S, Barner JC, Bohman TM, Rascati K, Lawson K, and Wilson JP. Use of antidepressants and the risk of type 2 diabetes mellitus: a nested case-control study. Int J Clin Pharm. 2012;34(3):432-8.

prednisolone and dexamethasone),[214] and immunosuppressive agents (especially tacrolimus and cyclosporine).[215]

2.3.6 Pathophysiology

Three distinct pathophysiologic processes can be attributed to the development of type 2 diabetes. These include resistance to insulin action in the peripheral tissue, defective insulin secretion, and increased hepatic glucose output.[216] Insulin resistance is believed to be the first step in the development of diabetes. Elevated levels of free fatty acids and pro-inflammatory cytokines – both secondary to weight gain and obesity – causes insulin resistance, thereby decreasing cellular transport of glucose, and increasing both hepatic glucose output and fat metabolism. This processes triggers increased production of insulin by pancreatic beta cells in order to maintain glucose homeostasis. The sustained hyperglycemia leads to dysfunction and subsequent death of the beta cells, causing insulin production to be insufficient to counteract the increased plasma glucose concentration.[217]

The pathophysiology of type 1 diabetes involves the autoimmune destruction of the pancreatic beta cells.[218]

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[214] Kwon S, and Hermayer KL. Glucocorticoid-induced hyperglycemia. Am J Med Sci. 2013;345(4):274-7.
[215] Penfornis A, and Kury-Paulin S. Immunosuppressive drug-induced diabetes. Diabetes Metab. 2006;32(5 Pt 2):539-46; Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant. 2007;7(6):1506-14.
[216] Seggelke S and Everhart B, "Management of type 2 diabetes."
[217] Ibid.
[218] Bluestone JA, Herold K, and Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293-300.

2.3.7 Demographic Risk Factors

Non-modifiable demographic factors such as male gender, older age, and certain race/ethnicity put people at increased risk of diabetes.[219]

According to the CDC's National Diabetes Statistics Report of 2014 which utilized data from the 2009 – 2012 NHIS, the prevalence of diagnosed and undiagnosed diabetes (type 1 or type 2) among adults aged 20 years and older was higher among men (13.6% or 15.5 million) compared to women (11.2% or 13.4 million).[220] A higher proportion of people with diabetes was also seen among people aged 65 years and older (25.9%) compared to those aged 45 – 64 years (16.2%), or 20 – 44 years (4.1%).[221]

After adjustment for age differences, and using data from the 2010 – 2012 NHIS and the 2012 Indian Health Service's National Patient Information Reporting System, the CDC reports that the proportion of people with diagnosed diabetes among American Indians/Alaska Natives (15.9%) was higher compared to the proportion of people with diagnosed diabetes among non-Hispanic blacks (13.2%), Hispanics (12.8%), Asian-Americans (9.0%) and non-Hispanic whites (7.6%).[222]

2.3.8 Signs, Symptoms, and Complications

The hallmark symptoms of diabetes are polydipsia (excessive thirst), polyuria (frequent urination), and polyphagia (increased hunger) which are related to the

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[219] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."
[220] Ibid.
[221] Ibid.
[222] Ibid.

hyperglycemia.[223] Diabetic patients are often asymptomatic for many years after which a gradual progression of symptoms and chronic complications of the disease sets in.[224] Other symptoms that may be present at diagnosis include irritability, fatigue, skin wounds, blurred vision, and vaginal infections.[225]

Acute complications of diabetes include hypoglycemia (abnormally low blood sugar level between 50-60 mg/dL), diabetic ketoacidosis (acute shortage of insulin, common in type 1 than type 2 diabetes), and hyperglycemic hyperosmolar syndrome (characterized by an altered sense of awareness of sensation, perception and interpretation of the surrounding). Chronic complications of diabetes are related to the cardiovascular and renal systems which significantly impair the activity of daily living, and include macrovascular complications (cerebrovascular disease, coronary heart disease, and peripheral vascular disease), and microvascular complications (retinopathy, nephropathy, and neuropathy).[226]

2.3.9 Diagnosis

Diabetes is diagnosed by a variety of laboratory methods, including through the fasting plasma glucose (FPG), the 2-hour value of the 75-g oral glucose tolerance test (OGTT), random plasma glucose (RPG), and glycated or glycosylated hemoglobin $A1_c$ (A1C). Diagnosis through the A1C method – endorsed by an International Expert Committee on diabetes (which includes the American Diabetes Association) – is the

[223] Hilaire ML, and Woods TM. Type 2 diabetes: A focus on new guidelines. Formulary. 2013;48(2):55.
[224] American Diabetes Association, "Standards of medical care in diabetes--2014."
[225] Ali N, *Diabetes and you: A comprehensive, holistic approach*.
[226] Ibid.

preferable and more accurate method due to convenience (because fasting is not required), and stability (A1C estimates the average blood glucose level over the past 2-3 months).[227] Furthermore, AIC is a strong predictor for subsequent development of diabetes,[228] and for complications arising from diabetes.[229]

Routine testing to detect type 2 diabetes and prediabetes is recommended in asymptomatic adults of any age who are overweight or obese, and who have one or more additional risk factor for diabetes (Table 2.19). Prediabetics are intermediate group of people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) who do not currently meet the criteria for clinical diagnosis of diabetes, but have an increased risk of developing full diabetes in the future.

In accordance with adult testing recommendations, and because the incidence of diabetes among US adolescents has substantially increased within the past decade,[230] routine testing within the health care setting should be initiated – beginning at age 10 – in asymptomatic children who are at increased risk of type 2 diabetes (i.e., who are

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[227] Sacks DB, Arnold M, Bakris GL, et al. Position statement executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care. 2011;34(6):1419-23.

[228] Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. Ibid.2010;33(7):1665-73; Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800-11; Ackermann RT, Cheng YJ, Williamson DF, and Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005-2006. Am J Prev Med. 2011;40(1):11-7.

[229] The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-86; Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.

[230] Dabelea D, D'Agostino RB, Jr., Mayer-Davis EJ, et al. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1 (autoimmune) diabetes. Diabetes Care. 2006;29(2):290-4.

overweight, have a family history of type 2 diabetes, belong to races/ethnicity with increased risk of diabetes, have signs or conditions associated with insulin resistance [acanthosis nigricans, hypertension, hyperlipidemia, etc.], and have a maternal history of GDM during the child's gestation).[231]

In type 1 diabetes, clinical-based routine testing is currently not recommended for low-risk asymptomatic individuals, but screening (through measurement of islet autoantibodies) should be considered in individuals who have relatives with type 1 diabetes.[232]

Table 2.18 summarizes the diagnostic methods and cut-off values in diabetes and prediabetes, while Table 2.19 summarizes the recommended steps that should guide testing of type 2 diabetes in asymptomatic adults.

[231] American Diabetes Association. Standards of medical care in diabetes--2014. Ibid.2014;37 Suppl 1:S14-80.
[232] Ibid.

Table 2.18: Criteria for the Diagnosis of Diabetes and Prediabetes in Adults			
Criteria	**Diabetes**	**Prediabetes**	**Comments**
A1C	≥6.5%	5.7-6.4%	The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay[a]
OR			
FPG	≥126 mg/dL (7.0 mmol/L)	100-125 mg/dL (5.6-6.9 mmol/L)	Fasting is defined as no caloric intake for at least 8 hours[a]
OR			
2-hour plasma glucose during an OGTT	≥200 mg/dL (11.1 mmol/L)	140-199 mg/dL (7.8-11 mmol/L)	The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]
OR			
RPG	≥200mg/dL (11.1 mmol/L)	NA	In patients with classic symptoms of hyperglycemia or hyperglycemic crisis

Source: American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37(Supplement 1):S14-S80.

Abbreviations: A1C, Glycated hemoglobin A_{1C}; NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial; FPG, Fasting plasma glucose; OGTT, Oral glucose tolerance test; WHO, World Health Organization; RPG, Random plasma glucose.

[a]In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Table 2.19: Diabetes Risk Factors and Criteria for Testing for Type 2 Diabetes in Asymptomatic Adults	
A	Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2)[a] and who have additional risk factors **Risk factors:** 1. Physical inactivity 2. First-degree relative with diabetes 3. High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) 4. Women who delivered a baby weighing >9 lb or were diagnosed with GDM 5. Hypertension (≥140/90 mmHg or on therapy for hypertension) 6. HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) 7. Women with polycystic ovary syndrome 8. A1C ≥5.7% or presence of prediabetes 9. Presence of other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)[b] 10. History of CVD
B	In the absence of the above criteria, testing for diabetes should begin at age 45 years.
C	If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

Source: American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37(Supplement 1):S14-S80.

Abbreviations: BMI, Body mass index; GDM, Gestational diabetes mellitus; HDL, High-density lipoprotein; A1C; Glycated hemoglobin A_{1C}; CVD, Cardiovascular disease.

[a]At-risk BMI may be lower in some ethnic groups.

[b]Acanthosis nigricans is a brown to black, poorly defined, velvety hyperpigmentation of the skin usually found in body folds such as the posterior and lateral folds of the neck, armpits, groin, navel, and forehead.

2.3.10 Prevention of Diabetes

Several RCTs have demonstrated the efficacy of intensive lifestyle modification and use of pharmacological agents (especially metformin) at significantly decreasing the rate of onset of type 2 diabetes in people at high risk of developing the disease.[233] Long-term follow-up of three particularly large studies of lifestyle intervention has shown sustained reduction in the rate of conversion from prediabetes to diabetes. The China Da Qing Diabetes Prevention Study showed a 43% risk reduction of diabetes at 20 years,[234] while the Finish Diabetes Prevention Study,[235] and the US Diabetes Prevention Program Outcomes Study,[236] respectively, showed a 43% risk reduction at 7 years, and a 34% risk reduction at 10 years of utilizing TLC. Of the therapeutic agents (e.g., metformin, α-glucosidase inhibitors, orlistat, and thiazolinediones) considered useful in the prevention of diabetes, long-term use of metformin has been shown to be particularly safe and tolerable,[237] and cost-effective.[238]

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[233] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403; Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. Ibid.2001;344(18):1343-50; Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20(4):537-44; Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, and Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97.

[234] Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371(9626):1783-9.

[235] Lindstrom J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Ibid.2006;368(9548):1673-9.

[236] Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Ibid.2009;374(9702):1677-86.

[237] Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2012;35(4):731-7.

In type 1 diabetes, clinical trial interventions using agents such as rituximab[239] and abatacept[240] are believed to be showing promising efficacy at slowing down the destruction of β-cells in individuals with evidence of recent-onset autoimmunity.

2.3.11 Therapeutic Management

Diabetes management should be patient specific and should involve collaborations from an interdisciplinary health care team that includes nurses, dieticians, physicians, and pharmacists.[241] Treatment strategy should involve taking into account the individual patient's comorbid conditions, ability to adhere to prescribed medications, and the cost associated with a chosen therapeutic option.[242]

The goals of controlling blood glucose are to avoid acute symptoms of hypoglycemia, avoid instability in blood glucose levels, and to prevent or delay the development of diabetes complications without adversely affecting quality of life.[243]

Once a patient is diagnosed with type 2 diabetes, lifestyle modifications including diet, weight loss (if needed), and exercise are encouraged. Metformin monotherapy should be started at, or soon after diagnosis unless contraindicated. The guidelines recommend checking A1C after 3 months of therapy, with the possibility of adding a

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[238] The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012;35(4):723-30.
[239] Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009;361(22):2143-52.
[240] Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;378(9789):412-9.
[241] Hilaire ML and Woods TM, "Type 2 diabetes: A focus on new guidelines."
[242] Ibid.
[243] Ibid.

second antidiabetic agent if therapy is not at goal. Possible second-line agents include sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, and insulin.[244]

The recommended pharmacological treatment with insulin therapy in most people with type 1 diabetes involves three approaches: 1) the use of multiple dose insulin injections or continuous subcutaneous insulin infusion therapy; 2) matching of prandial (with meal) insulin to carbohydrate intake, pre-prandial blood glucose, and anticipated activity; and 3) the use of insulin analogs (e.g., insulin glargine, insulin lispro, insulin aspart, etc.) in individuals experiencing problems with hypoglycemia.[245]

Recommendations for the management of type 2 diabetes, as jointly issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes are presented in Table 2.20. Table 2.21 summarizes the FDA- approved medications (excluding insulin) that are currently available for treating type 2 diabetes.

[244] Ibid.
[245] American Diabetes Association, "Standards of medical care in diabetes--2014."

Table 2.20: Recommendations for the Management of Type 2 Diabetes	
1.	Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes
2.	In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset
3.	If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3–6 months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin[a]
4.	A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences
5.	Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes

Source: American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37(Supplement 1):S14-S80.

[a]Second-line oral agents include sulfonylureas, thiazolidinediones, and dipeptidylpeptidase-4 (DPP-4) inhibitors.

Table 2.21: FDA-Approved Oral Medications Used in the Treatment of Type 2 Diabetes*					
Class	**Mechanism of Action**	**Drug**	**Brand Name**	**Available Strength (mg)#**	**Dosing^**
Alpha-glucosidase inhibitors[a]	Competitively blocks alpha-glucosidase enzyme, resulting in the slowing down of intestinal breakdown of carbohydrate and starch into glucose	Acarbose	Precose®	25, 50, 100 (Generic and Precose®)	Initial: 25 mg TID Max: 100 mg TID
		Miglitol	Glyset®	25, 50, 100 (Glyset®)	Initial: 25-50 mg TID Max: 100 mg TID
Biguanides[b]	-Inhibits hepatic glycogenolysis and gluconeogenesis -Enhances insulin sensitivity in muscle and fat	Metformin	Glucophage® Glucophage XR® Fortamet®(ER) Glumetza® (ER)	500, 850, 1000 (Generic and Glucophage®) 500, 750, 1000 (Generic XR) 500, 750 (Glucophage XR®) 500, 1000 (Fortamet® and Glumetza®)	Initial: 500 mg BID or 850 mg QD (XR=500 mg QD) Max: 2550 mg QD (XR=2000 mg QD)
Meglitinides[c]	They stimulate pancreatic insulin secretion	Nateglinide	Starlix®	60, 120 (Generic and Starlix®)	Initial: 120 mg TID Max: 120 mg TID
		Repaglinide	Prandin®	0.5, 1, 2 (Generic and Prandin®)	Initial: 0.5-4 mg QD Max: 16 mg QD
Sulfonylureas 1st generation[d]	They stimulate pancreatic insulin secretion	Chlorpropamide	NA	100, 250 (Generic)	Initial: 250 mg QD Max: 750 mg QD
		Tolbutamide	NA	500 (Generic)	Initial: 1-2g QD Max: 3g QD
		Tolazamide	NA	250, 500 (Generic)	Initial: 100-250 mg QD Max: 1g QD

Table 2.21: FDA-Approved Oral Medications Used in the Treatment of Type 2 Diabetes (Cont'd)*					
Class	**Mechanism of Action**	**Drug**	**Brand Name**	**Available Strength (mg)#**	**Dosing^**
Sulfonylureas 2nd generation[e]	They stimulate pancreatic insulin secretion	Glipizide	Glucotrol® Glucotrol XL® GlipiZIDE XL®	5, 10 (Generic and Glucotrol) 2.5, 5, 10 (Generic ER, GlipiZIDE XL® and Glucotrol XL®)	Initial: 5 mg QD (XL=5-10 mg QD) Max: 15-40 mg QD (XL=20 mg QD)
		Glibenclamide (Glyburide)	Diabeta® Glynase®	1.25, 1.5, 2.5, 3, 5, 6 (Generic) 1.25, 2.5, 5 (Diabeta®) 1.5, 3, 6 (Glynase®)	Initial: 1.25-5 mg QD Max: 20 mg QD
		Glimepiride	Amaryl®	1, 2, 4 (Generic and Amaryl®)	Initial: 1-2 mg QD Max: 8 mg QD
Thiazolidinedi-ones (Glitazones)[f]	Enhances insulin sensiti- vity in muscle and fat by increasing glucose trans- porter expression	Rosiglitazone	Avandia®	2, 4, 8 (Avandia®)	Initial: 4 mg QD Max: 8 mg QD
		Pioglitazone	Actos®	15, 30, 45 (Generic and Actos®)	Initial: 15-30 mg QD Max: 45 mg QD
Bile acid sequestrants	-May reduce hepatic insulin resistance leading to reduction in hepatic glucose production -May reduce intestinal glucose absorption	Colesevelam	Welchol®	625, 3750 (Welchol®)	Initial: 6 tab (3.75g) QD Or 3 tab (1.875g) BID Max: 3.75g QD

Table 2.21: FDA-Approved Oral Medications Used in the Treatment of Type 2 Diabetes (Cont'd)*					
Class	**Mechanism of Action**	**Drug**	**Brand Name**	**Available Strength (mg)#**	**Dosing^**
Amylin analog	-Decreases postprandial glucagon secretion and hepatic glucose production -Slows gastric emptying which leads to feelings of satiety	Pramlintide	SymlinPen 60® SymlinPen 120®	1500 mcg/1.5mL 2700 mcg/2.7mL (SubQ solutions)	Initial: 60 mcg QD, SubQ Max: 120 mcg QD, SubQ
Dipeptidyl peptidase-4 (DPP-4) inhibitors[g]	Inhibits breakdown of endogenous incretins resulting in increased secretion of insulin and decreased secretion of glucagon	Sitagliptin	Januvia®	25, 50, 100 (Januvia®)	100 mg QD
		Saxagliptin	Onglyza®	2.5, 5 (Onglyza®)	2.5-5 mg QD
		Linagliptin	Tradjenta®	5 (Tradjenta®)	5 mg QD
		Alogliptin	Nesina®	6.25, 12.5, 25 (Nesina®)	25 mg QD
Glucagon-like peptide-1 (GLP-1) agonists[h]	-Stimulate GLP-1 recept- ors, which increases insulin production in response to high blood glucose levels -Inhibit postprandial glucagon release and slow gastric emptying	Exenatide	Bydureon® Byetta 10 MCG Pen® Byetta 5 MCG Pen®	2mg (Bydureon®, SubQ suspension) 10 mcg/0.04mL (Byetta 10 MCG Pen®, SubQ solution) 5 mcg/0.02mL (Byetta 5 MCG Pen®, SubQ solution)	5-10 mcg BID (ER: 2mg once weekly)
		Liraglutide	Victoza®	18 mg/3mL (SubQ solution)	Initial: 0.6-1.2 mg QD Max: 1.8 mg QD

Table 2.21: FDA-Approved Oral Medications Used in the Treatment of Type 2 Diabetes (Cont'd)*					
Class	**Mechanism of Action**	**Drug**	**Brand Name**	**Available Strength (mg)#**	**Dosing^**
Dopamine agonist	Increases insulin sensitivity as a result of hypothalamic regulatory changes in metabolism	Bromocriptin	Cycloset®	0.8 (Cycloset®)	Initial: 0.8 mg QD Max: 4.8 mg QD

Sources: Lexicomp Online; 2013. US Food and Drug Administration. National Drug Code query-active ingredient; 2013. Hilaire ML, Woods TM. Type 2 diabetes: A focus on new guidelines. *Formulary.* 2013;48(2):55.

Abbreviations: QD, Daily; BID, Twice daily; TID, Three times daily; Max, Maximum; XR/ER/XL, Extended release tablet or capsule; NA, Not available; SubQ, Subcutaneously.

^All dosing are for adults.

#All dosage forms are immediate release tablets or capsules, unless otherwise stated.

*Several combination products exist, including pioglitazone/metformin, rosiglitazone/metformin, glipizide/metformin, glyburide/metformin, sitagliptin/metformin, linagliptin/metformin, saxagliptin/metformin, repaglinide/metformin, rosiglitazone/glimepiride, and pioglitazone/glimepiride.

[a]Includes voglibose (research product of Takeda Pharma; not yet FDA-approved).

[b]Includes phenformin, buformin (both withdrawn from the market due to toxic effects), and proguanil (not FDA-approved for diabetes but indicated as an antimalarial).

[c]Include mitiglinide (not yet FDA-approved for treating type 2 diabetes).

[d]Includes carbutamide and acetohexamide (both discontinued in the United States).

[e]Includes gliclazide, glibornuride, gliquidone, glisoxepide, and glycopyramide (either outdated, discontinued, or not presently available in the United States).

[f]Includes troglitazone (withdrawn from the market due to drug-induced hepatitis), netoglitazone, rivoglitazone, and ciglitazone (experimental agents).

[g]Includes vildagliptin (marketed in the European Union), dutogliptin, gemigliptin (both under development), and anagliptin (marketed in Japan).

[h]Includes albiglutide and taspoglutide (both under development).

2.3.12 Glycemic Control

Optimization of glycemic control is a central strategy in the management of diabetic nephropathy, retinopathy, and neuropathy. Lowering A1C to below or around 7% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease.[246] However, the target A1C should be chosen such that hypoglycemia and other adverse events of treatment are significantly minimized.[247] The importance of intensive glycemic control at delaying the onset of, or slowing down the progression of diabetic nephropathy,[248] diabetic retinopathy,[249] and diabetic neuropathy,[250] has been elucidated by several studies. However, CVD – a more common cause of death in populations with diabetes than microvascular complications – is less clearly impacted by levels of hyperglycemia, or by the intensity of glycemic control.[251]

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[246] Ibid.

[247] Ibid.

[248] Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376(9739):419-30; Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-39; Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. Ibid.2008;358(24):2560-72.

[249] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53; Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233-44.

[250] Ismail-Beigi F et al., "Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial."; Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103-17.

[251] American Diabetes Association, "Standards of medical care in diabetes--2014."

Several reasons may be responsible for the inability to reach target glycemic control in people with diabetes. More successful outcomes may be achieved by a reassessment of factors including the patient's income, health literacy, distress associated with the disease, depression, and competing demands, especially those related to family responsibilities and dynamics.[252] Other strategies that may be employed to enhance patient compliance and achieve more glycemic control include culturally appropriate and enhanced diabetes self-management education and support, co-management with a diabetes team, referral to a medical social worker for assistance with insurance coverage, or change in pharmacological therapy.[253] Initiation of, or increase in patient self-monitoring of blood glucose, utilization of continuous glucose monitoring, frequent contact with the patient, or referral to a mental health professional or physician with special expertise in diabetes may also be useful.[254]

2.3.13 Management of Diabetes Comorbidities

In addition to achieving a desirable glycemic control, special attention should be given to cardiovascular and lipid management in people with diabetes. Other management considerations should also include antiplatelet management (using aspirin 75–162 mg/day),[255] smoking cessation therapy,[256] management of diabetes-associated

[252] Ibid.
[253] Ibid.
[254] Ibid.
[255] Ibid.
[256] Voulgari C, Katsilambros N, and Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism. 2011;60(10):1456-64.

disease conditions such as diabetic foot ulcer,[257] hearing impairment,[258] obstructive sleep apnea,[259] fatty liver disease,[260] low testosterone in men,[261] periodontal disease,[262] certain cancers (e.g., liver, pancreas, colorectal, and breast),[263] fractures,[264] cognitive impairment,[265] and depression.[266]

Cardiovascular Management

CVD is a macrovascular complication of diabetes. It is the major cause of morbidity and mortality in people with diabetes, contributing substantially to the direct and indirect medical cost associated with diabetes treatment.[267] Moreover, the two

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[257] Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132-73.
[258] Bainbridge KE, Hoffman HJ, and Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. Ann Intern Med. 2008;149(1):1-10.
[259] West SD, Nicoll DJ, and Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax. 2006;61(11):945-50.
[260] El-Serag HB, Tran T, and Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126(2):460-8.
[261] Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care. 2010;33(6):1186-92.
[262] Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, and Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. J Diabetes Complications. 2006;20(1):59-68.
[263] Suh S, and Kim KW. Diabetes and cancer: is diabetes causally related to cancer? Diabetes Metab J. 2011;35(3):193-8; Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674-85.
[264] Janghorbani M, Van Dam RM, Willett WC, and Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol. 2007;166(5):495-505; Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. Osteoporos Int. 2007;18(4):427-44.
[265] Cukierman T, Gerstein HC, and Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia. 2005;48(12):2460-9; Biessels GJ, Staekenborg S, Brunner E, Brayne C, and Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64-74.
[266] Anderson RJ, Freedland KE, Clouse RE, and Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24(6):1069-78.
[267] American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Ibid.2013;36(4):1033-46.

common conditions coexisting with diabetes (i.e., hypertension and dyslipidemia) are risk factors for CVD, with diabetes itself being an independent CVD risk factor.[268]

A blood pressure goal of <140/<80mmHg is recommended for people with comorbid diabetes and hypertension.[269] Studies indicate that people with diabetes have better cardiovascular outcomes and reduced mortality when their BP is less than 115/75mmHg, whereas a systolic blood pressure above 120mmHg is a recipe for long-term end-stage renal disease (ESRD).[270]

The management of people with comorbid hypertension and diabetes often involve a combination of non-pharmacological and pharmacological therapeutic options. Non-pharmacological management should include therapeutic lifestyle changes such as weight loss through physical exercise, moderation of alcohol consumption, smoking cessation, and the implementation of the Dietary Approaches to Stop Hypertension (DASH) dietary pattern (including increased intake of fruits and vegetables, and reduction of salt).[271] Significant cardiovascular outcomes has been achieved, and therapy for patients with comorbid diabetes and hypertension is optimal when the first choice

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[268] American Diabetes Association, "Standards of medical care in diabetes--2014."
[269] Ibid.
[270] Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560-72; Lewington S, Clarke R, Qizilbash N, Peto R, and Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13; Stamler J, Vaccaro O, Neaton JD, and Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16(2):434-44.
[271] U.S. Department of Health and Human Services. "Your Guide to Lowering your Blood Pressure with DASH." Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, 2006.

therapeutic agent includes either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).[272]

Nevertheless, multiple drug therapy (using two or more agents at maximal doses) is generally required to achieve blood pressure targets in this group of patients.[273] Table 2.22 summarizes the major classes of drugs used in treating hypertension in people with diabetes.

Table 2.22: FDA-Approved Medications Used in the Treatment of Hypertension in Patients with Diabetes

Drug	Brand Name	Available Strength (mg)[#]
ACE-Inhibitors[a]		
Benazepril	Lotensin®	5, 10, 20, 40 (Generic) 10, 20, 40 (Lotensin®)
Captopril	NA	12.5, 25, 50, 100
Enalapril	Vasotec® Epaned®	2.5, 5, 10, 20 (Generic and Vasotec®) 150mL of 1mg/mL (Epaned®)
Fosinopril	NA	10, 20, 40
Lisinopril	Prinivil® Zestril®	5, 10, 20 (Prinivil®) 2.5, 5, 10, 20, 30, 40 (Generic and Zestril®)
Moexipril	Univasc®	7.5, 15 (Generic and Univasc®)
Perindopril	Aceon®	2, 4, 8 (Generic) 4, 8 (Aceon®)
Quinapril	Accupril®	5, 10, 20, 40 (Generic and Accupril®)
Ramipril	Altace®	1.25, 2.5, 5, 10 (Generic and Altace®)
Trandolapril	Mavik®	1, 2, 4 (Generic and Mavik®)
ARBs		
Azilsartan	Edarbi®	40, 80 (Edarbi®)
Candesartan	Atacand®	4, 8, 16, 32 (Generic and Atacand®)
Eprosartan	Teveten®	600 (Generic), 400, 600 (Teveten®)

[272] Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care. 1998;21(4):597-603; Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, and Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med. 1998;338(10):645-52; Schrier RW, Estacio RO, Mehler PS, and Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol. 2007;3(8):428-38.

[273] American Diabetes Association, "Standards of medical care in diabetes--2014."

Table 2.22: FDA-Approved Medications Used in the Treatment of Hypertension in Patients with Diabetes (Cont'd)		
Drug	**Brand Name**	**Available Strength (mg)[#]**
ARBs cont'd		
Irbesartan	Avapro®	75, 150, 300 (Generic and Avapro®)
Losartan	Cozaar®	25, 50, 100 (generic and Cozaar®)
Olmesartan	Benicar®	5, 20, 40 (Benicar®)
Telmisartan	Micardis®	20, 40, 80 (Micardis®)
Valsartan	Diovan®	40, 80, 160, 320 (Diovan®)
Calcium Channel Blockers (Dihydropyridine)[b]		
Amlodipine	Norvasc®	2.5, 5, 10 (Generic and Norvasc®)
Clevidipine	Cleviprex®	0.5 mg/mL (50 mL, 100 mL)(Cleviprex®)
Felodipine	Plendil®	2.5, 5, 10 (Generic and Plendil®)
Isradipine	Dynacirc® CR	2.5, 5 (Generic) 5, 10 (Dynacirc CR®)
Nicardipine	Cardene IV® Cardene SR®	20, 30 (Generic) 30, 60 (Cardene SR®) 20 mg (200 mL), 40 mg (200 mL)(Cardene IV®) 2.5 mg/mL (10 mL)(Generic and Cardene IV®)
Nifedipine	Adalat CC® Afeditab CR® Nifediac CC® Nifedical XL® Procardia® Procardia XL®	10 (Procardia®) 10, 20 (Generic) 30, 60 (Nifedical XL®, Nifediac CC®, Afeditab CR®) 30, 60, 90 (Generic ER, Procardia XL®, Adalat CC®) 90 (Nifediac CC®)
Nimodipine	Nymalize®	30 (Generic) 60 mg/20 mL (473 mL)(Nymalize®)
Nisoldipine	Sular®	8.5, 17, 20, 25.5, 30, 34, 40 (Generic) 8.5, 17, 34 (Sular®)

Source: Lexicomp Online; 2013. US Food and Drug Administration. National Drug Code query-active ingredient; 2013.

Abbreviations: FDA, Food and Drug Administration; ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker; NA, Not Available; IV, Intravenous.

[#]All dosage forms are oral immediate release tablets or capsules, unless otherwise stated. CR, SR, CC, CR, and XL are extended or controlled release dosage forms.

[a]Class includes cilazapril, imidapril, and zofenopril (marketed internationally but not currently approved for use in the United States).

[b]Class members not currently marketed in the US includes aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, efonidipine, lacidipine, lercanidipine, manidipine, nilvadipine, nitrendipine, and pranidipine.

Lipid Management

Patients with diabetes have an increased prevalence of lipid abnormalities that can contribute to their high risk of CVD.[274] Annual screening for dyslipidemia is encouraged by the ADA to achieved an LDL-C and TG goals of <100mg/dL and <150mg/dL, respectively. An HDL-C goals of >40 mg/dL (men) or >50 mg/dL (women) is desired; however, the main goal of therapy is focused on reducing LDL-C levels.[275] Treatment of diabetic dyslipidemia is usually achieved with a combination of lifestyle modifications and pharmacotherapy using statins and other lipid-lowering agents. Unless contraindicated, statins should be started, regardless of initial LDL-C levels, in all type 2 diabetic patients that are aged 40 years and older and with at least one cardiovascular risk factor (e.g., family history of CVD, hypertension, smoking, dyslipidemia, and albuminuria).[276] [The new ATP IV guideline recommends using a moderate intensity statin in individuals 40 – 75 years of age with diabetes who have LDL-C of 70-189 mg/dL. A high intensity statin should be considered in this group of patients if the 10-year ASCVD risk is ≥ 7.5%. Meanwhile, consideration should be given to patient preferences, evaluation of the ASCVD risk-reduction benefit versus potentials for adverse effects, and drug-drug-interactions when deciding to initiate, continue, or intensify therapy in those less than 40 years or those older than 75 years].[277]

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[274] Ibid.
[275] Ibid.
[276] Ibid.
[277] Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

Several clinical trials have demonstrated the effectiveness of statins at reducing LDL-C levels and improving cardiovascular outcomes in both primary and secondary prevention, including among the diabetic sub-population.[278]

[278] Pyorala K et al., "Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S)."; Collins R, Armitage J, Parish S, Sleigh P, and Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16; Goldberg RB et al., "Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators."; Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care. 2006;29(6):1220-6; Sever PS, Poulter NR, Dahlof B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Ibid.2005;28(5):1151-7; Colhoun HM et al., "Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial."; Knopp RH et al., "Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN)."

2.4 SECTION IV: STATINS AND INCIDENT DIABETES MELLITUS

2.4.1 Introduction

Statins are generally well tolerated and are believed to have minimal adverse effects.[279] However, some of the most common adverse effects associated with statin therapy include myopathies, elevation of liver enzymes, and very rarely, rhabdomyolysis.[280] Discontinuation or reduction in the dose of statin treatment usually leads to resolution of these adverse effects.[281] For many years, however, there has been debate as to whether statins are indeed as safe as reported in clinical trials.[282]

Recently, the US FDA have expanded the warning section of the label for all statins to suggest an increased risk of incident diabetes mellitus as a result of increases in glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG).[283] Recent evidence also suggests that the use of statins can result in an increased risk for the development of diabetes, possibly through modification of glucose homeostasis.[284] Meanwhile, the

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279 Pasternak RC et al., "ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins."
280 Ibid.
281 Bruckert E et al., "Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study."
282 Alberton M, Wu P, Druyts E, Briel M, and Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM. 2012;105(2):145-57.
283 Food and Drug Administration, "FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs".
284 Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."; Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."; Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Ridker PM, Pradhan A, MacFadyen JG, Libby P, and Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary

mechanism by which statins have differential effects on glucose homeostasis still remain unclear;[285] however, statins are thought to worsen glycemic control and increase fasting plasma glucose and insulin resistance, thereby possibly leading to diabetes mellitus.[286]

Only a few observational studies have evaluated the association between statin use and the risk of new onset diabetes. Results from these studies have also been inconsistent. To date, only twelve population-based observational studies have examined the association between statin therapy and incidence of diabetes.[287] These observational

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prevention: an analysis from the JUPITER trial. Lancet. 2012;380(9841):565-71; Thongtang N et al., "Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation."; Koh KK et al., "Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients."; Sabatine MS et al., "High-dose atorvastatin associated with worse glycemic control: a PROVE-IT TIMI 22 substudy."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

[285] Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."; Waters DD, Ho JE, DeMicco DA, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. J Am Coll Cardiol. 2011;57(14):1535-45.

[286] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; Mabuchi H, Higashikata T, Kawashiri M, et al. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. J Atheroscler Thromb. 2005;12(2):111-9; Sasaki J, Iwashita M, and Kono S. Statins: beneficial or adverse for glucose metabolism. Ibid.2006;13(3):123-9.

[287] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; ibid.; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; ibid.; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; ibid.; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; ibid.; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; ibid.; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."; ibid.; Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."; Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."; Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."

studies included eight retrospective cohort studies,[288] two prospective cohort studies,[289] and two case-control studies.[290] Overall, the strength of association linking statin therapy to incident diabetes in RCTs, meta-analyses of RCTs and observational studies is weak or moderate. Moreover, other evidence indicates a protective effect of statins on diabetes. The section below evaluates the available evidence linking statin therapy to increased risk of incident diabetes. Evidences from randomized control trials, meta-analyses of RCTs, and observational studies are examined.

2.4.2 Randomized Control Trials

Several major (i.e., recruiting large number of participants and with follow-up period greater than 1 year) placebo-controlled statin trials in primary,[291] and secondary

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[288] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; ibid.; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; ibid.; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."; ibid.; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; ibid.; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; ibid.; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; ibid.; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; ibid.

[289] Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."; ibid.; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

[290] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."; ibid.; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

[291] "Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)."; Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."; Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."; Shepherd J et al., "Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial."; Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-

prevention,[292] suggests a moderate association (i.e., increase in risk that is less than 50%) between statin therapy and increased risk of incident diabetes. Similar results were seen in trials comparing intensive and moderate statin doses[293] (See Table 2.23). While the results of some of the earlier trials published between 1995 and 2000 demonstrated a non-statistically significant, moderately protective effect of statin therapy on incident diabetes (as observed in the WOSCOP,[294] AFCAPS/TexCAPS,[295] LIPID,[296] and GISSI-P

Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Ibid.2003;361(9364):1149-58; Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Ibid.2006;368(9542):1155-63; Ridker PM et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein."

[292] "MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial."; "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)."; "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."; Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. Ibid.2007;357(22):2248-61; Tavazzi L et al., "Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial."; "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)."

[293] Cannon CP et al., "Intensive versus moderate lipid lowering with statins after acute coronary syndromes."; de Lemos JA et al., "Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial."; LaRosa JC et al., "Intensive lipid lowering with atorvastatin in patients with stable coronary disease."; Pedersen TR et al., "High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial."; Armitage J et al., "Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial."

[294] Shepherd J et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group."

[295] Downs JR et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study."

[296] "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group."

trials[297]), the majority of later studies, albeit with a mixture of statistical significance and non-significance, showed a tendency for statins to be associated with an increased odds of diabetes. These increased odds of diabetes ranged from 3 percent, observed in the 4S study,[298] to 32 percent, recorded in the PROSPER study.[299]

In particular, the results of the PROSPER study,[300] published in 2002, and similar findings by the JUPITER study,[301] published in 2008, showed that pravastatin and rosuvastatin were significantly associated with relatively large increase in the odds of diabetes of 32 percent and 26 percent, respectively. These later findings kick-started a series of discussions about the safety of statins and the need to weigh the benefit of cardiovascular protection against the risk of incident diabetes from statin use. In combination with other evidence, the FDA was prompted to take action, resulting to a change in the labeling of all statins, in February 2012, to include risk of increases in HbA1c and/or fasting plasma glucose that could lead to drug-induced diabetes mellitus.[302]

The incidences of diabetes reported by the results of the aforementioned RCTs - which primarily examined statins' beneficial effects on cardiovascular outcomes in

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297 "Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)."
298 "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)."
299 Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Ibid.2002;360(9346):1623-30.
300 Ibid.
301 Ridker PM et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein."
302 Food and Drug Administration, "FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs".

primary and secondary prevention trials – has prompted other investigators, through meta-analyses of RCTs and observational studies, to either confirm or reject the hypothesis that statins are associated with increased risk of statin-induced diabetes.

Table 2.23: Incident Diabetes Reported in Major Randomized Controlled Trials of Statins										
Trials	**Statin (dose per day)**	**Control**	**Total N**	**Non-DM at baseline (%)**	**Number (statin)**	**Number (control)**	**New DM cases**	**New DM (statin)**	**New DM (control)**	**Odds Ratio (95% C.I.)**
WOSCOPS[a]	Pravastatin 40mg	Placebo	6,595	5,974 (91)	2,999	2,975	168	75	93	0.79 (0.58-1.10)
AFCAPS/ TexCAPS[b]	Lovastatin 20-40mg	Placebo	6,605	6,211 (94)	3,094	3,117	146	72	74	0.98 (0.70-1.38)
ALLHAT-LLT[c]	Pravastatin 40mg	Usual Care	10,355	6,087 (59)	3,017	3,070	450	238	212	1.15 (0.95-1.41)
PROSPER[d]	Pravastatin 40mg	Placebo	5,804	5,023 (87)	2,510	2,513	292	165	127	1.32 (1.03-1.69)
ASCOT-LLA[e]	Atorvastatin 10mg	Placebo	10,305	7,773 (75)	3,910	3,863	288	154	134	1.14 (0.89-1.46)
MEGA[f]	Pravastatin 10-20mg + diet	Diet + Usual Care	7,832	6,086 (78)	3,013	3,073	336	172	164	1.07 (0.86-1.35)
JUPITER[g]	Rosuvastatin 20mg	Placebo	17,802	17,802 (100)	8,901	8,901	486	270	216	1.26 (1.04-1.51)
HPS[h]	Simvastatin 40mg	Placebo	20,536	14,573 (72)	7,291	7,282	628	335	293	1.15 (0.98-1.35)
4S[i]	Simvastatin 20-40mg	Placebo	4444	4242 (95)	2116	2126	391	198	193	1.03 (0.84-1.28)
LIPID[j]	Pravastatin 40mg	Placebo	9014	6997 (78)	3496	3501	264	126	138	0.91 (0.71-1.71)
CORONA[k]	Rosuvastatin 20mg	Placebo	5011	3534 (71)	1771	1763	188	100	88	1.14 (0.84-1.55)

Table 2.23: Incident Diabetes Reported in Major Statin Randomized Controlled Trials (Cont'd)										
Trials	**Statin Dose/day**	**Control**	**Total N**	**Non-DM at baseline (%)**	**Number (statin)**	**Number (control)**	**New DM cases**	**New DM (statin)**	**New DM (control)**	**Odds Ratio (95% C.I.)**
GISSI-HF[l]	Rosuvastatin 10mg	Placebo	4,574	3,378 (74)	1,660	1,718	440	225	215	1.10 (0.89-1.35)
GISSI-P[m]	Pravastatin 20mg	Usual care	4,271	3,460 (81)	1,743	1,717	201	96	105	0.89 (0.67-1.20)
Intensive Dose vs. Moderate Dose Statin Trials										
	Intensive statin dose/ Moderate statin dose (dose per day)		**Total N**	**Non-DM at baseline (%)**	**Number (ISD)**	**Number (MSD)**	**New DM cases**	**New DM (ISD)**	**New DM (MSD)**	**Odds Ratio (95% C.I.)**
PROVE IT-TIMI 22[n]	Atorvastatin 80mg/ pravastatin 40mg		4,162	3,395 (82)	1,707	1,688	200	101	99	1.01 (0.76-1.34)
A to Z[o]	Simvastatin 40mg, Simvastatin 80mg/ placebo, simvastatin 20mg		4,497	3,504 (78)	1768	1,736	112	65	47	1.37 (0.94-2.01)
TNT[p]	Atorvastatin 80mg/ atorvastatin 10mg		10,001	7,595 (76)	3,798	3,797	776	418	358	1.19 (1.02-1.38)
IDEAL[q]	Atorvastatin 80mg/ simvastatin 20mg or simvastatin 40mg		8,888	7,461 (84)	3,737	3,724	449	240	209	1.15 (0.95-1.40)
SEARCH[r]	Simvastatin 80mg/ simvastatin 20mg		12,064	10,797 (89)	5,398	5,399	1,212	625	587	1.07 (0.95-1.21)

Table 2.23: Incident Diabetes Reported in Major Statin Randomized Controlled Trials (Cont'd)

Sources: Navarese EP, Swiatkiewicz I, Sukiennik A, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol.* 2013;111(8):1123. Preiss D, Sabatine MS, Braunwald E, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA.* 2011;305(24):2556-2564. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet.* 2010;375(9716):735-742.

Abbreviations: N, Sample size; DM, Diabetes mellitus; C.I., Confidence interval; ISD, Intensive statin dose; MSD, Moderate statin dose.

[a]Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. WOSCOPS Group. *N Engl J Med.* 1995;333(20):1301-1307 [**WOSCOPS**, West of Scotland Coronary Prevention Study].

[b]Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA.* 1998;279(20):1615-1622 [**AFCAPS/TexCAPS**, Air Force/Texas Coronary Atherosclerosis Prevention Study].

[c]Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The ALLHAT-LLT. *JAMA.* 2002;288(23):2998-3007 [**ALLHAT-LLT**, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial].

[d]Shepherd J, Blauw GJ, Murphy MB, et al. (PROSPER): a randomised controlled trial. *Lancet.* 2002;360(9346):1623-1630 [**PROSPER**, Pravastatin in Elderly Individuals at Risk of Vascular Disease].

[e]Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the ASCOT-LLA: a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158 [**ASCOT-LLA**, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm].

[f]Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (**MEGA** Study): a prospective randomised controlled trial. *Lancet.* 2006;368(9542):1155-1163 [**MEGA**, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese].

[g]Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-2207 [**JUPITER**, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin].

[h]MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360(9326):7-22 [**HPS**, Heart Protection Study].

[i]Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the 4S. *Lancet.* 1994;344(8934):1383-1389 [**4S**, Scandinavian Simvastatin Survival Study].

Table 2.23: Incident Diabetes Reported in Major Statin Randomized Controlled Trials (Cont'd)

[j]Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The LIPID Study Group. *N Engl J Med.* 1998;339(19):1349-1357 [**LIPID**, Long-Term Intervention with Pravastatin in Ischaemic Disease].

[k]Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357(22):2248-2261 [**CORONA**, Controlled Rosuvastatin Multinational Study in Heart Failure].

[l]Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372(9645):1231-1239 [**GISSI-HF,** Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure: Italy, double-blind trial of 3.9 years follow-up conducted in 326 centers, men and women aged 18 years and older with symptomatic heart failure with average age of 68 years].

[m]Results of the low-dose (20 mg) pravastatin GISSI-P trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI-P Investigators. *Ital Heart J.* 2000;1(12):810-820 [**GISSI-P**, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione].

[n]Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495-1504 [**PROVE IT-TIMI 22**, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22: Double-blind trial conducted in 8 countries and 349 centers with a mean follow-up of 2 years, men and women with acute coronary syndrome].

[o]de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA.* 2004;292(11):1307-1316 [**A to Z,** Aggrastat to Zocor trial: Double-blind trial conducted in 322 centers of 41 countries, men and women with acute coronary syndrome aged 21-80 years with baseline LDL-C of 112 mg/dL].

[p]LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352(14):1425-1435 [**TNT**, Treating to New Targets clinical trial].

[q]Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005;294(19):2437-2445 [**IDEAL**, Incremental Decrease in End Points Through Aggressive Lipid Lowering].

[r]Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet.* 2010;376(9753):1658-1669 [**SEARCH**, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine].

2.4.3 Meta-Analysis of RCTs

Shortly after the publication of the 2008 JUPITER study that showed pravastatin was associated with a 26 percent increase in the odds of new onset diabetes, Rajpathak et al. (2009) published the results of a meta-analysis of six RCTs, comprising WOSCOPS, HPS, ASCOT-LLA, LIPID, CORONA, and, of course, JUPITER, to investigate the hypothesis that statin therapy is associated with increased risk of diabetes.[303] Their results showed that statin use was associated with a 13 percent significant increase in diabetes risk (RR=1.13, C.I.=1.03-1.23, p=0.008), with no evidence of heterogeneity across trials when the WOSCOP trial (which originally showed a protective effect of statin against diabetes) was excluded from the analyses. Upon inclusion of the WOSCOP trial, a non-significant increase of 6 percent in diabetes risk (RR=1.06, 95% C.I.=0.93-1.25, p=0.38) was associated with statin use, with evidence of heterogeneity across trials.

The results of subsequent meta-analyses has shown an overall tendency of statin therapy to be associated with an increased risk in diabetes, with one meta-analysis recording a non-statistically significant increase of diabetes or worsening of insulin sensitivity,[304] while others showed a statistically significant increased risk of diabetes.[305] For example, Mills et al. (2011) investigated the risk of statin-associated incident diabetes

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303 Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."

304 Baker WL et al., "Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis."

305 Navarese EP et al., "Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus."; Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."; Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."; Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."

in a meta-analysis of 17 large RCTs comprising 111,003 participants. Study results showed that the odds of incident diabetes increased by 9 percent in statin users compared to controls (OR=1.09, 95% C.I.=1.02-1.16), with little heterogeneity between trials.[306]

Similarly, a meta-analyses of 13 large RCTs comprising 91, 140 patients by Sattar et al. (2010) showed that statin therapy was associated with a 9 percent increase in the odds of incident diabetes (OR=1·09, 95% C.I.=1·02–1·17), with little heterogeneity between trials.[307] A sub-analyses of the association between the individual statins and incident diabetes showed that rosuvastatin (3 RCTs) was associated with the highest increase in diabetes odds of 18 percent, while atorvastatin (1 RCT), simvastatin (2 RCTs), and pravastatin (6 RCTs) were associated with a 14 percent, 11 percent, and 3 percent increase in the odds of incident diabetes, respectively. Moreover, lovastatin (1 RCT) was associated with a 2 percent protective effect.

A more recent meta-analysis of 55 RCTs comprising 113,698 patients conducted by Naci et al. (2013) also showed that statin therapy was associated with a 9 percent increase in the odds of incident diabetes compared to controls (OR=1.09, 95% C.I.=1.02-1.16), with little heterogeneity between trials, and with no statistically detectable differences between individual statins in terms of diabetes mellitus incidence.[308]

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[306] Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."
[307] Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."
[308] Naci H et al., "Comparative tolerability and harms of individual statins: A study-level network meta-analysis of 246 955 participants from 135 randomized controlled trials."

However, another recent meta-analysis of 17 RCTs comprising 113,394 patients by Navarese et al. (2013) showed a mixed result with respect to the type and daily dose of statin used.[309] Though not statistically significant, pravastatin 40mg was shown to be associated with the lowest increase in the odds of new onset diabetes compared with placebo (OR=1.07, 95% C.I.=0.86 – 1.30), while rosuvastatin 20mg was found to be associated with the highest increase in the odds of new onset diabetes when compared with placebo (OR=1.25, 95% C.I.=0.82 – 1.90). The overall results of this meta-analysis indicated a non-statistically significant protective effect, or a non-statistically significant increase in the odds of diabetes associated with different types and doses of statin, with odds ratio ranging from 0.9-1.25 (i.e.,10 percent reduction in the odds of diabetes to 25 percent increase in the odds of diabetes).

In summary, evidence from meta-analysis of RCTs leaned towards statins being significantly associated with a moderate increase in risk of diabetes.

2.4.4 Observational Studies

Since the FDA's announcement of safety labeling changes to all statins in February 2012, ten observational studies have been published that tested the hypothesis of whether increased risk of incident diabetes is associated with statin therapy. These studies examined the association between incident diabetes and statins as a class, as well as the effects of various types and doses of statins on the risk of incident diabetes. The observational studies that were published after the statin labeling changes included seven

[309] Navarese EP et al., "Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus."

retrospective cohort studies,[310] two prospective cohort studies,[311] and one case-control study.[312] Five of these aforementioned studies examined the effects of statins as a class on incident diabetes. Four of the five studies concluded that statins were significantly associated with increased risk of new onset diabetes,[313] whereas one study found a non-significant increase in risk.[314]

Moreover, two studies conducted before the statin labeling change concluded that statins were generally associated with an increased risk of incident diabetes.[315] A 2009 retrospective cohort study found fasting plasma glucose to be significantly increased among statin users compared to non-users,[316] whereas a 2004 case-control study found a non-statistically significant increased risk of incident diabetes with statin use.[317]

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[310] Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."

[311] Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

[312] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."

[313] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

[314] Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

[315] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

[316] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

[317] Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

In addition to examining the risk of incident diabetes in statins as a class, some of these observational studies also examined whether certain types and doses of statins are associated or not associated with increased risk of incident diabetes. Evidence from the observational studies suggested that simvastatin and atorvastatin had the greatest potential to be significantly associated with increased risk of incident diabetes, while fluvastatin and lovastatin had the least potential to be significantly associated with an increased risk. Pravastatin and rosuvastatin appears to have moderate potential to be significantly associated with increased risk. None of the observational studies evaluated the association of pitavastatin and incident diabetes.

With respect to statin doses and its association with incident diabetes, a 2013 retrospective cohort study found no significant difference in the proportion of patients on intensive dose statin and those on moderate dose statin that had new onset diabetes.[318]

Overall, the evidence from observational studies appears to indicate that statins are generally associated with a moderate increased risk of incident diabetes, with a majority of statins recording a statistically significant increase in risk, while a minority recorded a non-statistically significant increase in risk. Some statins showed both a statistically significant and a statistically non-significant protective effect against diabetes. Table 2.24 summarizes the study characteristics and results of observational studies examining the association between statin use and reports of incident diabetes, while Table 2.25 summarizes the relative risk (i.e., hazard ratio and odds ratio), including

[318] Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."

the statistical significance of the relative risk (i.e., Table 2.26) of the association between different types of statins and incident diabetes that are reported in observational studies.

Table 2.24: Incident Diabetes Reported in Observational Studies						
	Title	**Study cohort**	**Region**	**Outcomes**	**Statistical Analysis**	**Results**
RETROSPECTIVE COHORT						
Ko, 2013[a]	Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins	17,080 hospitalized patients with MI, 8540 matched pairs, mean age=78 years	Canada	NOD compared between patients prescribed IDS vs. MDS	Kaplan-Meier survival curves between the two group were compared using stratified log rank test	At 5 years, no significant difference in the proportion of IDS patients (13.6%) and MDS patient (13%) that had NOD (p=0.19)
Danaei, 2013[b]	Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival	285,864 men and women aged 50-84 years without DM	United Kingdom	Incident T2D between statin initiators and non-initiators	Estimated the observational analog of ITT hazard ratio of DM for initiators vs. non-initiators by fitting a Cox model	Statin initiation was significantly associated with increased risk of T2D. HR=1.14 (95% C.I.=1.10-1.19)
Carter, 2013[c]	Risk of incident diabetes among patients treated with statins: population based study	471,250 patients, median age=73 years, 54% women	Canada	Incident diabetes between other statins and pravastatin	Time to event analyses using Cox proportional hazard regression to estimate relation between use of statin and incident diabetes	Compared to pravastatin, there was significant increased risk of NOD with atorvastatin, rosuvastatin, and simvastatin; but not with fluvastatin or lovastatin

Table 2.24: Incident Diabetes Reported in Observational Studies (Cont'd)						
	Title	**Study cohort**	**Region**	**Outcomes**	**Statistical Analysis**	**Results**
RETROSPECTIVE COHORT (Cont'd)						
Ma, 2012[d]	The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study	15,637 elderly hypertensive and dyslipidemic patients, 65-80 years, mean age=75 years, 57% women	Taiwan	Effect of statins on the development of NOD compared to non-users	Cox regression model to estimate time to development of NOD for each statin	Compared to non-users, there was significant increased risk of NOD with lovastatin and simvastatin; significant decreased risk with atorvastatin and rosuvastatin; and no difference in risk with fluvastatin and pravastatin
Zaharan, 2012[e]	Statins and risk of treated incident diabetes in a primary care population	239,628 patients who received statin monotherapy	Ireland	Incident diabetes between statin users and non-users	Time to NOD was compared between statin users and non-users using the Cox proportional hazard regression model	Statin use was associated with a significant increased risk of NOD (HR=1.20, 95% C.I.=1.17-1.23)

Table 2.24: Incident Diabetes Reported in Observational Studies (Cont'd)						
	Title	**Study cohort**	**Region**	**Outcomes**	**Statistical Analysis**	**Results**
RETROSPECTIVE COHORT (Cont'd)						
Ma, 2012[f]	Statins and new-onset diabetes: A retrospective longitudinal cohort study	16,027 patients with hypertension and dyslipidemia aged 20-84 years, mean age=60 years, 54% women	Taiwan	Effect of statins on the development of NOD compared to non-users	Cox regression model to estimate time to development of NOD for each statin	Compared to non-users, there was significant increased risk of NOD with pravastatin; significant decreased risk with fluvastatin, rosuvastatin and lovastatin; and no difference in risk with atorvastatin and simvastatin
Wang, 2012[g]	Statins, risk of diabetes, and implications on outcomes in the general population	42,060 men and women aged ≥45 years and ≥55 years, respectively	Taiwan	Incident diabetes between statin users and non-users	-Kaplan-Meier survival curves between statin users and non-users were compared using stratified log rank test -Cox regression model to estimate time to development of NOD between statin users and non-users	-Cumulative incidence of diabetes were significantly higher in statin users (22.7%) compared to non-users (20.8%)($p<0.001$) -NOD significantly increased with statin use (HR=1.15, 95% C.I.=1.08-1.22)

Table 2.24: Incident Diabetes Reported in Observational Studies (Cont'd)						
	Title	**Study cohort**	**Region**	**Outcomes**	**Statistical Analysis**	**Results**
RETROSPECTIVE COHORT (Cont'd)						
Sukhija, 2009[h]	Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients	345,417 patients, mean age=61 years, 94% males, 6% diabetic	USA Veterans Affairs	Effect of statins on FPG in nondiabetic and diabetic patients	Multiple regression to compare difference in FPG change between statin users and non-users	FPG significantly increased in statin users compared to non-users among diabetic ($p<0.0001$) and non-diabetic populations ($p<0.0001$)
PROSPECTIVE COHORT						
Izzo, 2013[i]	Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk	4,750 hypertensive, non-diabetic patients, mean age=59 years, 58% men	Italy	Risk of incident DM with statin use	Hazard functions for incident DM were generated by Cox regression analysis comparing participants taking or not taking statins	Statins were not significantly associated with increased risk of incident DM (HR=1.03, 95% C.I.=0.79-1.35)
Culver, 2012[j]	Statin use and risk of diabetes mellitus in postmenopausal women in the WHI	153,840 postmenopausal women aged 50-79 years, mean age=63 years	USA 40 centers	Risk of incident DM with statin use	Cox proportional hazards model used to estimate HRs of DM by statin medication use	Statin use was significantly associated with increased risk in incident DM (HR=1.48, 95% C.I.=1.38-1.59)

Table 2.24: Incident Diabetes Reported in Observational Studies (Cont'd)						
	Title	**Study cohort**	**Region**	**Outcomes**	**Statistical Analysis**	**Results**
CASE-CONTROL						
Chen, 2013[k]	Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country	1065 female patients with NOD and 10650 matched-controls, mean age=61 years	Taiwan	Risk of incident DM with statin use	Multiple logistic regression to examine whether statin use was an independent risk factor of NOD	Increased risk of DM was associated with use of atorvastatin, rosuvastatin, simvastatin, and pravastatin compared to non-users.
Jick, 2004[l]	Statins and newly diagnosed diabetes	588 cases and 2063 matched controls aged 30-79 years, mean age of 59 years, 51% male	United Kingdom	Odds of incident DM with statin use	Conditional logistic regression	Statins were not significantly associated with increased risk of DM (OR=1.1, 95% C.I.=0.8-1.4)

Abbreviations: MI, Myocardial infarction; NOD, New-onset diabetes; IDS, Intensive-dose statin; MDS, Moderate-dose statin; DM, Diabetes mellitus; T2D, Type 2 diabetes; ITT, Intention-to-treat; HR, Hazard ratio; C.I., Confidence interval; FPG, Fasting plasma glucose; WHI, Women's Health Initiative.

[a]Ko DT, Wijeysundera HC, Jackevicius CA, Yousef A, Wang J, Tu JV. Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins. *Circ Cardiovasc Qual Outcomes.* 2013;6(3):315-322.

[b]Danaei G, García Rodríguez LA, Fernandez Cantero O, Hernán MA. Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care.* 2013;36(5):1236.

[c]Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ.* 2013;346:f2610.

[d]Ma T, Chang MH, Tien L, Liou YS, Jong GP. The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study. *Drugs Aging.* 2012;29(1):45-51.

Table 2.24: Incident Diabetes Reported in Observational Studies (Cont'd)

[e]Zaharan NL, Williams D, Bennett K. Statins and risk of treated incident diabetes in a primary care population. *Br J Clin Pharmacol.* 2013;75(4):1118-1124.

[f]Ma T, Tien L, Fang C-L, Liou Y-S, Jong G-P. Statins and new-onset diabetes: a retrospective longitudinal cohort study. *Clin Ther.* 2012;34(9):1977-1983.

[g]Wang KL, Liu CJ, Chao TF, et al. Statins, risk of diabetes, and implications on outcomes in the general population. *J Am Coll Cardiol.* 2012;60(14):1231-1238.

[h]Sukhija R, Prayaga S, Marashdeh M, et al. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. *J Investig Med.* 2009;57(3):495-499.

[i]Izzo R, de Simone G, Trimarco V, et al. Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk. *Nutr Metab Cardiovasc Dis.* 2013;23(11):1101-1106.

[j]Culver AL, Merriam PA, Rahilly-Tierny C, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med.* 2012;172(2):144.

[k]Chen CW, Chen TC, Huang KY, Chou P, Chen PF, and Lee CC. Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country. PLoS One. 2013;8(8):e71817.

[l]Jick SS, Bradbury BD. Statins and newly diagnosed diabetes. *Br J Clin Pharmacol.* 2004;58(3):303-309.

Table 2.25: Summary of the Association between Different Types of Statins and Incident Diabetes Reported in Observational Studies		
Study	**Statin**	**Adjusted HR (95% C.I.)**
RETROSPECTIVE COHORT		
Danaei, 2013[a]	Atorvastatin	1.22 (1.12-1.32)
	Fluvastatin	1.02 (0.69-1.50)
	Pravastatin	1.01 (0.84-1.21)
	Rosuvastatin	1.11 (0.89-1.38)
	Simvastatin	1.14 (1.09-1.20)
Carter, 2013[b]	Atorvastatin	1.22 (1.15-1.29)
	Fluvastatin	0.95 (0.81-1.11)
	Lovastatin	0.99 (0.86-1.14)
	Rosuvastatin	1.18 (1.10-1.26)
	Simvastatin	1.10 (1.04-1.17)
Ma, 2012[c]	Atorvastatin	0.77 (0.72-0.83)
	Fluvastatin	1.00 (0.87-1.16)
	Lovastatin	1.36 (1.24-1.48)
	Pravastatin	1.07 (0.94-1.23)
	Rosuvastatin	0.66 (0.52-0.83)
	Simvastatin	1.30 (1.14-1.47)
Zaharan, 2012[d]	Atorvastatin	1.25 (1.21-1.28)
	Fluvastatin	1.04 (0.91-1.18)
	Pravastatin	1.02 (0.98-1.06)
	Rosuvastatin	1.42 (1.33-1.52)
	Simvastatin	1.14 (1.06-1.23)
Ma, 2012[e]	Atorvastatin	1.15 (0.96-1.35)
	Fluvastatin	0.46 (0.33-0.61)
	Lovastatin	0.70 (0.59-0.83)
	Pravastatin	1.30 (1.13-1.56)
	Rosuvastatin	0.54 (0.39-0.76)
	Simvastatin	1.11 (0.92-1.32)
PROSPECTIVE COHORT		
Culver, 2012[f]	Atorvastatin	1.61 (1.26-2.06)
	Fluvastatin	1.61 (1.35-1.92)
	Lovastatin	1.35 (1.19-1.55)
	Pravastatin	1.63 (1.43-1.87)
	Simvastatin	1.41 (1.25-1.61)

Table 2.25: A Summary of the Association between Different Types of Statins and Incident Diabetes Reported in Observational Studies (Cont'd)		
Study	**Statin**	**Adjusted OR (95% C.I.)**
CASE-CONTROL		
Chen, 2013[g]	Atorvastatin	2.80 (1.74-4.49)
	Pravastatin	3.41 (1.66-7.04)
	Rosuvastatin	4.69 (2.78-7.92)
	Simvastatin	4.09 (2.52-6.64)
Jick, 2004[h]	Pravastatin	0.70 (0.40-1.20)
	Simvastatin	1.00 (0.70-1.30)

Abbreviations: HR, Hazard ratio; OR, Odds ratio; C.I., Confidence interval.

[a]Danaei G, García Rodríguez LA, Fernandez Cantero O, Hernán MA. Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care.* 2013;36(5):1236 [Reference = non-statin users: adjusted for age, sex, LDL-C, HDL-C, BMI, systolic BP, alcohol use, smoking, medications such as antihypertensives, NSAIDs, β-blockers, hormone replacement therapy, steroids, antidepressants, immunosuppressants, chemotherapy, and medical conditions including COPD, atrial fibrillation, depression, hypothyroidism, osteoporosis, psoriasis, rheumatoid arthritis, and chronic pancreatitis].

[b]Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ.* 2013;346:f2610 [Reference = pravastatin: adjusted for age, sex, year of cohort entry, recent acute coronary syndrome, chronic coronary artery disease, Charlson score, previous use of thiazide, nitroglycerin, angiotensin receptor blocker, β-blocker, hormones and analogues].

[c]Ma T, Chang MH, Tien L, Liou YS, Jong GP. The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study. *Drugs Aging.* 2012;29(1):45-51 [Reference = non-statin users: adjusted for age, sex, concomitant medication usage (aspirin, diuretics, β-blockers, calcium channel blockers, ACE-inhibitors, ARBs, α-blockers, and vasodilators), and mean dose of statin].

[d]Zaharan NL, Williams D, Bennett K. Statins and risk of treated incident diabetes in a primary care population. *Br J Clin Pharmacol.* 2013;75(4):1118-1124 [Reference = non-statin users: adjusted for gender, age group, prescriptions for oral corticosteroids, antipsychotics, antihypertensives, nitrates, and lipid lowering agents such as ezetimibe, omega-3, fibrates, niacin].

[e]Ma T, Tien L, Fang C-L, Liou Y-S, Jong G-P. Statins and new-onset diabetes: a retrospective longitudinal cohort study. *Clin Ther.* 2012;34(9):1977-1983 [Reference = non-statin users: adjusted for age, sex, concomitant medications such as aspirin, diuretics, β-blockers, calcium channel blockers, ACE-inhibitors, ARBs, α-blockers, and vasodilators, and mean dose of statin].

Table 2.25: A Summary of the Association between Different Types of Statins and Incident Diabetes Reported in Observational Studies (Cont'd)

[f]Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med.* 2012;172(2):144-152 [Reference = non-statin users: adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of CVD at baseline].

[g]Chen CW, Chen TC, Huang KY, Chou P, Chen PF, Lee CC. Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an asian country. *PLoS One.* 2013;8(8):e71817 [Reference = non-statin users: adjusted for gender, diseases such as hypertension, CHD, diabetes, hyperlipidemia, atrial fibrillation, CKD, obesity, PAD, medications such as non-statin lipid lowering drugs, aspirin, ACE-Is, TG-lowering medications, hormone therapy, SES, geographic region, and urbanization level of residence].

[h]Jick SS, Bradbury BD. Statins and newly diagnosed diabetes. *Br J Clin Pharmacol.* 2004;58(3):303-309 [Reference = non-statin users: adjusted for BMI, hypertension, steroid use, smoking, and number of GP visits within 3 years preceding the index date. Matched on gender, age, practice area of physician, index date, and length of history of patients in the database].

Table 2.26: A Summary of Table 2.25 Showing the Statistical Significance of the Hazard Ratios and Odds Ratios of the Association between Different Statin Types and Incident Diabetes Obtained from Observational Studies

Statin	**Increased Risk**		**Protective Effect**	
	Significant	**Not-significant**	**Significant**	**Not-significant**
Atorvastatin	*****	*	*	
Fluvastatin	*	**	*	**
Lovastatin	**		*	*
Pravastatin	***	***		*
Rosuvastatin	***	*	**	
Simvastatin	******	*		*
Sub-total	**20**	**8**	**5**	**5**
Total	**28**		**10**	

*One count of observational study in which the stated statin showed increased risk or protective effect.

2.5 SECTION V: STUDY RATIONALE, STUDY PURPOSE, STUDY OBJECTIVES AND HYPOTHESES, AND STUDY AIMS

2.5.1 Study Rationale

The benefits of statins in both primary and secondary prevention of cardiovascular diseases are well documented in several studies. The recent change to statin labeling by the FDA to suggest an increased risk of diabetes through increases in A1C and plasma glucose level have prompted several investigators to assess the hypothesis of whether statins are truly diabetogenic. Most of the evidence from RCTs, meta-analyses of RCTs, and observational studies suggests that statins are moderately associated with increased risk; however, results of these associations are not consistent. While a majority of the results (with a mixture of statistical and non-statistical significance) indicates a moderate increase in risk, some studies suggest a protective effect of statins on diabetes.

Due to the inconsistency in the results obtained from previous studies, this observational study was conducted to further confirm or reject the hypothesis that statins are associated with increased risk of diabetes mellitus. In addition, this study was being undertaken because the majority of published observational studies examining the association between statin therapy and incident diabetes were carried out using non-US data. Even more importantly, several of the observational studies failed to account for the influence of certain important variables such as obesity, statin dosage intensity, and

hyperlipidemia that may confound the association between statin therapy and the development of incident diabetes.

Overall, the results from this study will provide further evidence as to the diabetogenic nature of statins. This information may provide additional guidance to clinicians in their decision to continue to use statins in patients with comorbid hypertension, dyslipidemia and cardiovascular diseases who are at high risk of developing diabetes.

2.5.2 Study Purpose

This study has two primary purposes. The first purpose of this study was to examine whether the development of incident diabetes differed between two exposure groups (i.e., between statin users or the exposed group and non-statin users or the unexposed group). The second purpose of this study was to examine whether the development of incident diabetes differed by the intensity of the statin dosage (i.e., intensive-dose statin vs. moderate-dose statin) to which subjects were exposed.

Both of these study purposes were accomplished by using two statistical approaches suitable for a retrospective cohort design. First, this study used survival analysis to compare the survival time (i.e., time between first drug use and the first diagnosis of diabetes) between statin users and non-statin users, between users of each statin type and non-statin users, and between intensive-dose statin users and moderate-dose statin users. Second, this study used a binary logistic regression analysis to compare incidence of diabetes mellitus between statin users and non-statin users, between users of

each statin type and non-statin users, and between intensive-dose statin users and moderate-dose statin users.

Both of these analyses were conducted while controlling for demographic variables (i.e., age and gender) and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, statin medication adherence, diabetogenic medications, and Charlson comorbidity index [CCI] score) that were appropriate for each statistical analysis.

2.5.3 Study Objectives and Hypotheses

The present study has 12 objectives. The specific study objectives with hypotheses for each objective are as follows:

Objective 1: To assess whether demographic characteristics (i.e., age and gender) differ between statin users and non-statin users.

$\mathbf{H_{1a}}$: Statin users will have a significantly higher mean age compared to non-statin users.

$\mathbf{H_{1b}}$: There is a significant association between exposure group (i.e., statin users and non-statin users) and gender.

Objective 2: To assess whether hyperlipidemia diagnosis differs between statin users and non-statin users.

$\mathbf{H_{2}}$: The proportion of statin users with a hyperlipidemia diagnosis will be significantly higher compared to that of non-statin users.

Objective 3: To assess whether obesity diagnosis differs between statin users and non-statin users**.**

$H_{0(3)}$: There is no significant difference in the proportion of statin users and non-statin users who have an obesity diagnosis.

Objective 4: To assess whether hypertension diagnosis differs between statin users and non-statin users**.**

H_4: The proportion of statin users with a hypertension diagnosis will be significantly higher compared to that of non-statin users.

Objective 5: To assess whether the mean number of prescriptions for all diabetogenic medications and the mean number of prescriptions for each diabetogenic medication (i.e., thiazide diuretics, β-blockers, antipsychotics, antidepressants, immunosuppressants, and glucocorticoids) differ between statin users and non-statin users.

$H_{0(5a)}$: There is no significant difference in the mean number of prescriptions for all diabetogenic medications between statin users and non-statin users.

$H_{0(5b)}$: There is no significant difference in the mean number of thiazide diuretic prescriptions for statin users and non-statin users.

$H_{0(5c)}$: There is no significant difference in the mean number of β-blocker prescriptions for statin users and non-statin users.

$H_{0(5d)}$: There is no significant difference in the mean number of antipsychotic prescriptions for statin users and non-statin users.

$H_{0(5e)}$: There is no significant difference in the mean number of antidepressant prescriptions for statin users and non-statin users.

$H_{0(5f)}$: There is no significant difference in the mean number of immunosuppressant prescriptions for statin users and non-statin users..

$H_{0(5g)}$: There is no significant difference in the mean number of glucocorticoid prescriptions for statin users and non-statin users.

Objective 6: To compare the mean CCI score between statin users and non-statin users.

$H_{0(6)}$: There is no significant difference in the mean CCI score between statin users and non-statin users.

Objective 7: To assess whether medication adherence (using MPR) differs among users of each statin type, and between intensive-dose statin users and moderate-dose statin users.

$H_{0(7a)}$: There is no significant difference in mean medication possession ratio (MPR) among users of each statin type.

H_{7b}: The mean medication possession ratio (MPR) will be significantly lower among intensive-dose statin users compared to moderate-dose statin users.

Objective 8 (Survival Analysis – Log-rank test and Kaplan-Meier Curves): To assess whether survival times (i.e., time to occurrence of diabetes) differ between statin users and non-statin users, among users of each statin type, and between intensive-dose statin users and moderate-dose statin users.

H_{8a}: Statin users will have a shorter survival time compared to non-statin users.

$H_{0(8b)}$: There is no significant difference in the mean survival time among users of each statin type.

H_{8c}: Intensive-dose statin users will have a shorter survival time compared to moderate-dose statin users.

Objective 9 (Survival Analysis – Cox Regression): To assess whether survival times differ between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score).

H_{9a}: Statin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

H_{9b}: Atorvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

H_{9c}: Fluvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

H_{9d}: Lovastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

H_{9e}: Pravastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

H_{9f}: Rosuvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

H_{9g}: Simvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

Objective 10 (Survival Analysis – Cox Regression): To assess whether survival times differ between intensive-dose statin users and moderate-dose statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, medication adherence, diabetogenic medication use, and CCI score).

H_{10}: Intensive-dose statin users will have a significantly shorter survival time compared to moderate-dose statin users while controlling for age, gender, and clinical covariates.

Objective 11 (Binary Logistic Regression): To assess whether incidence of diabetes differs between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score).

H_{11a}: The proportion of statin users with incident diabetes will be significantly higher compared to that of non-statin users.

H_{11b}: The proportion of statin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

H_{11c}: The proportion of atorvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

H_{11d}: The proportion of fluvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

H_{11e}: The proportion of lovastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

H_{11f}: The proportion of pravastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

H_{11g}: The proportion of rosuvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

H_{11h}: The proportion of simvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Objective 12 (Binary Logistic Regression): To assess whether incidence of diabetes differs between intensive-dose statin users and moderate-dose statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, medication adherence, diabetogenic medication use, and CCI score).

H_{12}: The proportion of intensive-dose statin users with incident diabetes will be significantly higher than that of moderate-dose statin users while controlling for age, gender and clinical covariates.

2.5.4 Study Aims

The 12 study objectives presented above are summarized by the following four study aims:

Aim 1: To compare the demographic (i.e., age and gender) and clinical characteristics (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score) between statin users and non-statin users (Objectives 1 – 6).

Aim 2: To compare medication adherence among users of each statin type, and between intensive-dose statin users and moderate-dose statin users (Objective 7).

Aim 3: Using survival analysis, to compare time to diabetes (or survival time) between statin users and non-statin users, between users of each statin type and non-statin users, and between intensive-dose statin users and moderate-dose statin users (Objectives 8 – 10).

Aim 4: Using binary logistic regression analysis, to compare incidence of diabetes between statin users and non-statin users, between users of each statin type and non-statin users, and between intensive-dose statin users and moderate-dose statin users (Objectives 11 & 12).

CHAPTER 3: METHODOLOGY

3.1 CHAPTER OVERVIEW

This section provides a detailed description of the study design (i.e., study population, study timeline, formation of the retrospective study cohorts, inclusion and exclusion criteria), data source (description of the *MarketScan*® data elements, coding of the diagnosis and procedure codes in the *MarketScan*® database), sample size calculation, study variables and the data analysis procedures.

3.2 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The study protocol submission was granted an IRB waiver by the Office of Research Support of The University of Texas at Austin's Institution Review Board because a secondary analysis of de-identified data does not meet the criteria to be considered human subjects research.

3.3 STUDY DESIGN

The study utilized a retrospective cohort design using an administrative claims database containing patients' pharmacy and medical claims to answer the research question of whether statin therapy was associated with an increased risk of diabetes incidence. Other investigators have used a retrospective cohort design (with survival analysis[319] and binary logistic regression analysis[320] procedures) to assess the association between drug exposure and incident diabetes in observational studies.

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[319] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate

3.3.1 Study Population

The base population for this study consisted of patients in the *MarketScan* database period of January 1, 2003 and December 31, 2004.

The following inclusion/exclusion criteria applied to the study population:

- ✓ Aged 20 – 63 years at index date (the index date for the statin and the non-statin groups was defined as the date of the first prescription claim for a statin or a non-statin drug, starting from July 1, 2003. In other words, the index drugs were identified within the index period of July 1, 2003 and January 1, 2004).
- ✓ Did not have a diagnosis of diabetes mellitus (ICD-9-CM codes 250.xx) in the pre-index period (the pre-index period for the statin and the non-statin groups was defined as a period of six months before the statin or the non-statin drug index dates). The six months of pre-index period was to ensure only incident diabetes cases were being measured;
- ✓ Continuously enrolled during the pre-index period and for at least one year after the index date;
- ✓ Patients who were 65 years and older were excluded due to the possibility of dual eligibility for private/public insurance and Medicare, and the consequent possibility of incomplete information.

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possible bias due to differential survival."; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

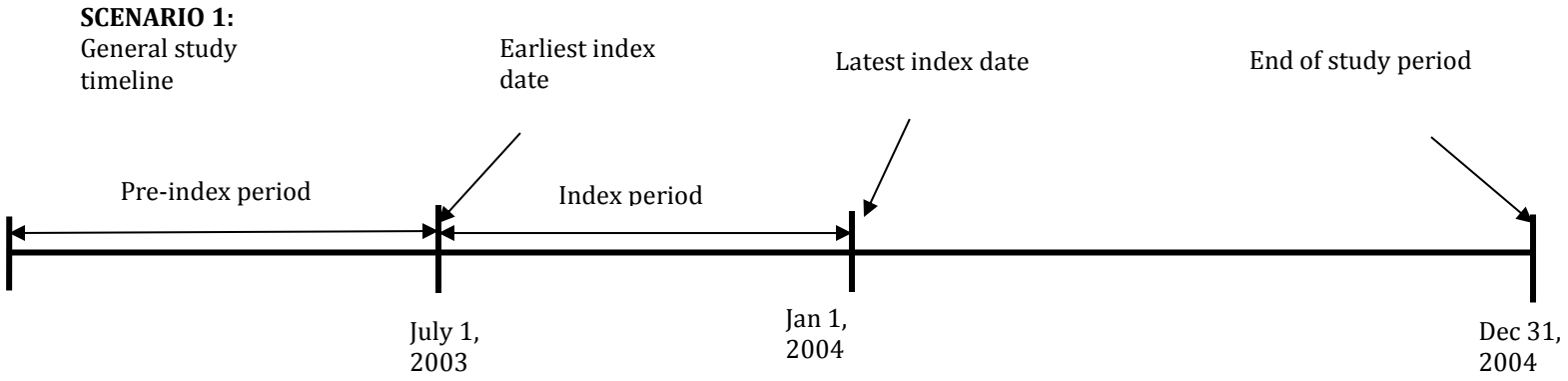
[320] Khoza S. "Use of antidepressant agents and the incidence of type 2 diabetes mellitus: A methodological comparison." Dissertation, The University of Texas at Austin, 2011.

3.3.2 Study Timeline

The overall timeframe for the study was the *MarketScan* data period between January 1, 2003 and December 31, 2004. Subjects were eligible for study inclusion if they had continuous enrollment during the pre-index period and also had a minimum continuous enrollment period of 12 months after the index medication. Subjects were allowed to enter the statin or the non-statin cohort any time from July 1, 2003, the earliest index date, until January 1, 2004, the latest index date. Subjects may therefore have different index dates and follow-up periods due to the open nature of the cohort entry. However, each index date was preceded by a six months of pre-index period for the purpose of excluding subjects with previous diagnosis of diabetes or previous use of the index medication. Subjects were allowed to exit either the statin or the non-statin cohort by a diagnosis of diabetes or by reaching the end of the study period without a diagnosis of diabetes.

Figure 3.1 illustrates the study timeline where one scenario depicts an ideal situation in which the index date was July 1, 2003 (Scenario 1), while the others (Scenarios 2 & 3) depict the follow-up and study inclusiveness of two subjects with different enrollment and index dates. The end of the study period (i.e., Dec 31, 2004) represented the enrollment end dates for all three scenarios.

Figure 3.1: Study Timeline



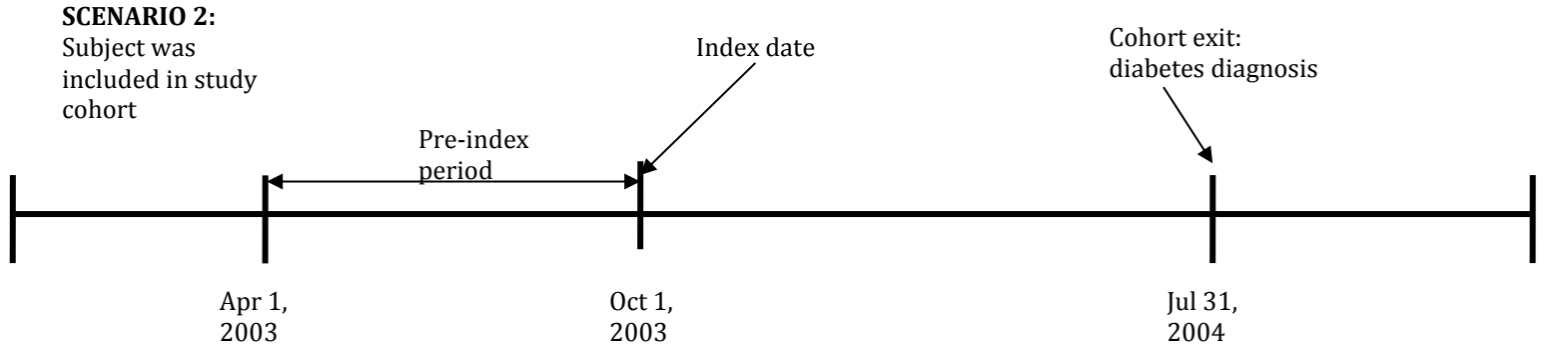
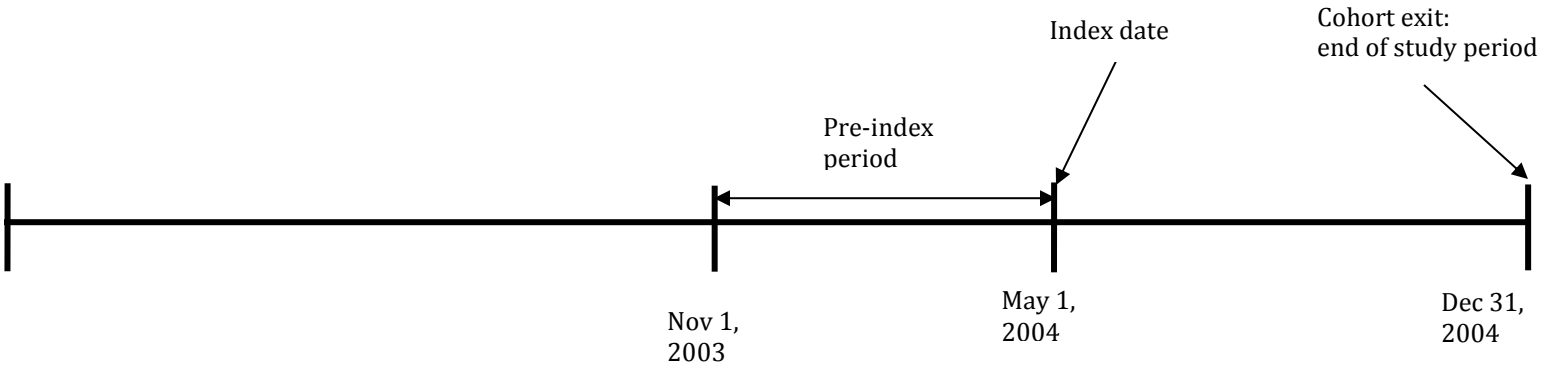


Figure 3.1: Study Timeline (cont'd)

SCENARIO 3:
Subject was excluded from the study cohort because continuous enrollment after the index date was less than a year



3.3.3 Retrospective Cohort Design

3.3.3.1 Overview

Cohort studies are longitudinal, observational studies that follow a group of people with shared characteristics, called 'a cohort,' through a defined period of time in order to observe a given outcome of interest at the end of the observation period.[321] Cohort studies can be performed prospectively (looking from the present to the future), or retrospectively (looking from the past to the present).[322] The measure of association in a cohort design is often expressed as a risk ratio called the relative risk (RR).[323]

The retrospective cohort design (also known as historic cohort study) is a cohort study sub-type where medical records of patients that were collected in the past are now being analyzed in the present with the aim of establishing and comparing two groups of people (i.e., the exposed and unexposed) on an outcome of interest. The two cohorts, who should be free of the disease of interest at baseline, are then 'followed-up' (i.e., from the receipt of the index medication to the end of the observation period) in order to determine their relative risk of developing the outcome of interest (here, diabetes).[324]

3.3.3.2 Formation of Cohorts

In the retrospective cohort design, two cohorts of patients were formed from the retrospective data. The first cohort, called statin users (or the exposed group) were those

[321] Euser AM, Zoccali C, Jager KJ, and Dekker FW. Cohort studies: prospective versus retrospective. Nephron Clin Pract. 2009;113(3):c214-7.
[322] Ibid.
[323] Ibid.
[324] Ibid.

patients who received a statin medication; while the second cohort, called non-statin users (or the unexposed group) were those patients who did not receive any statin medication. These two cohorts of people were then 'followed up' to determine their relative risk of developing incident diabetes.

Cohort 1: Statin Users

Statin users (or the exposed group) were those who received any statin medication including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin (pitavastatin is not included because it was approved after 2004, the study endpoint). The presence of any of these medications was determined using the FDA's National Drug Code (NDC) (see section 3.4.4 for the full description of the NDC code).

Because new users of statin drugs (i.e., no statin use in the six months prior to the first statin prescription claim) was desired in the cohort, the index date for statin users was defined as the date of the first prescription claim for any statin, starting from July 1, 2003. Thus, the earliest index date for any statin user was July 1, 2003, while the latest index date was January 1, 2004. This translated to an index period of between July 1, 2003 and January 1, 2004. Moreover, due to the open enrollment nature of the cohort, subjects had different index dates. The statin user cohort was then followed until they exited the cohort. Cohort exit (or end of follow-up) was defined as the occurrence of one of the following, whichever occurred first: (i) manifestation of the outcome of interest (i.e., diabetes); or (ii) reaching the end of the study period (i.e., December 31, 2004) without manifesting the outcome of interest.

Cohort 2: Non-Statin Users

The non-statin users were defined as subjects who did not receive a statin prescription during the observation period. The non-statin users as defined in this study have been used as the unexposed group in previous observational studies examining the association between statin therapy and incidence of diabetes mellitus.[325]

Similar to the statin users, non-statin users were identified within the index period of July 1, 2003 and January 1, 2004. This cohort was also followed until: (i) manifestation of diabetes; or (ii) end of follow-up period (December 31, 2004) without manifestation of diabetes.

3.3.3.3 Inclusion/Exclusion Criteria

In addition to the eligibility criteria set for the whole study population, the following additional sets of inclusion/exclusion criteria were set for statin users (cohort 1) and non-statin users (cohort 2):

[325] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

Cohort 1: Statin Users

- ✓ Received at least one statin prescription for atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin.[326]
- ✓ New statin user (i.e., had no prescription for a statin medication in the six months before the index date. The earliest index date was July 1, 2003);
- ✓ Did not fill a statin prescription that was combined with any of the non-statin lipid lowering agents such as bile-acid sequestrants (cholestyramine, colesevelam and colestipol), fibrates (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil), nicotinic acid or niacin, and ezetimibe;

In addition, subjects who switched the index statin type to a different statin type were analyzed based on the intention-to-treat principle, while subjects who switched the index statin dosage intensity to a different dosage intensity level were analyzed based on whether they ever received an intensive-dose statin during the observation period, or whether they received a moderate-dose statin throughout the observation period.

[326] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

Cohort 2: Non-Statin Users

- ✓ Not a statin user (i.e., did not fill prescription for any statin drug during the observation period).
- ✓ Did not fill prescription for a statin that is combined with any of the non-statin lipid lowering agents.

3.3.3.4 Statistical Methodology

The retrospective cohort design was analyzed using two different statistical methods. Survival analysis was used when the dependent variable of interest (i.e., survival time) is continuous in nature. This analysis strategy had been used in previous retrospective cohort designs that examined the association between drug exposure and incident diabetes mellitus.[327] A binary logistic regression analysis was used when the dependent variable of interest (incidence of diabetes: yes/no) is binary or dichotomous in nature. This alternate strategy for analyzing a retrospective cohort design had been used in a study that examined the association between antidepressant exposure and incident type 2 diabetes.[328]

3.3.3.4.1 Survival Analysis

Survival analysis is a statistical procedure used in modeling data that contains censored data on the outcome variable of interest. The outcome variable of interest is

[327] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Khoza S, Barner JC, Bohman TM, Rascati K, Lawson K, and Wilson JP. Use of antidepressant agents and the risk of type 2 diabetes. Eur J Clin Pharmacol. 2012;68(9):1295-302.
[328] Khoza S, "Use of antidepressant agents and the incidence of type 2 diabetes mellitus: A methodological comparison."

called the survival time. It is defined as the time (in days, weeks, months, or years) from when an individual is exposed to the factor of interest (e.g., statins) until an event (e.g., diabetes) occurs. The survival time gives the time that an individual has 'survived' over some follow-up period after an exposure of interest. The event is often referred to as a 'failure' because the event of interest usually is death, disease incidence, or some other negative individual experience. However, some survival times may be positive event, such as the time to return to work after an elective surgical procedure.[329]

In order to fully understand survival analysis, it is desirable to give a brief description of the key concepts, statistical procedures and notations associated with survival analysis. These include: (i) analytical problems such as "censoring," a concept that is primarily the distinguishing feature of survival analysis; (ii) mathematical concepts such as the survival function and the hazard function; and (iii) analytical methods such as the Kaplan-Meier estimator, the log-rank test, and the Cox proportional hazards regression (and its assumptions), tools that are used in comparing the survival experience of two or more groups.[330]

Censoring

Most survival analyses must consider a key analytical problem called censoring. Censoring occurs when we have some information about individual survival time but we do not know the survival time exactly. For a prospective cohort study, censoring may

[329] Kleinbaum DG, and Klein M. "Introduction to survival analysis." Chap. 1 In *Survival analysis: A self-learning text*. Statistics for biology and health, 4-15. New York, NY: Springer, 2012.
[330] Ibid.

occur when a person does not experience the event before the study ends, or when a person is lost to follow-up during the study period. In a retrospective cohort study design, censoring may mean discontinuation of an exposure of interest before the person experiences the event of interest.[331]

A table of survival data should contain a variable indicating censorship (0) or failure (1). Thus, a person who does not fail (i.e., does not get the event during the observation period), must have been censored either before or at the end of the study. Although data can be left-censored (i.e., the true survival time is less than or equal to the observed survival time), or assume some other forms of censoring; however, most survival data are right-censored.[332] Right censoring means that the true survival time is equal to or greater than the observed survival time. In other words, it means the complete survival time interval, which is unknown, has been cut-off at the right side of the observed survival time interval. This is the whole point of conducting survival analysis: to estimate the true survival time.

The Survival Function

The survival function, denoted by *S(t)*, gives the probability that a person survives longer than some specified time *t*. In other words, *S(t)* gives the probability that the random variable *T* exceeds the specified time *t*. The capital *T* is the random variable for a person's survival time. Its possible values include all nonnegative numbers (i.e., $T \geq 0$).

[331] Ibid.
[332] Ibid.

The small letter *t* denotes any specific value of interest for the random variable *T*.[333] For example, if we are interested in evaluating whether a person survives more than 5 years after undergoing cancer therapy, small *t* equals 5; we then ask whether capital *T* exceeds 5. Thus, the main purpose of the survival function is to help in estimating the survival probabilities for the different values of the observed survival time *t*.[334]

The survival function has the following theoretical characteristics:

(i) they are nonincreasing; that is, they decrease as *t* increases;

(ii) at time $t = 0$, $S(t) = S(0) = 1$. This means that the probability of surviving past the beginning of the study (when no one has experienced the event yet) is 1;

(iii) at time $t = \infty$, $S(t) = S(\infty) = 0$. This means that, theoretically, if the study period increased without limit, eventually nobody would survive, and the survival curve would eventually fall to zero.[335]

The Hazard Function

The hazard function, denoted by *h(t)*, gives the instantaneous potential per unit time for the event to occur, given that the individual has survived up to time *t*.[336] In contrast to the survival function which focuses on 'not failing,' the hazard function focuses on 'failing;' that is, on the event occurring. In mathematical terms, the hazard function (Figure 3.2) is written as:

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[333] Ibid.
[334] Ibid.
[335] Ibid.
[336] Ibid.

Figure 3.2: The Hazard Function

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$$

In words, the hazard function translates to: *h(t)* equals the limit, as Δt approaches zero, of a conditional probability statement about survival, divided by Δt, where Δt denotes a small interval in time. The conditional probability (the numerator) gives the probability that a person's survival time, *T*, will lie in the interval between *t* and $t + \Delta t$, given that the survival time is greater than or equal to *t*.[337]

The hazard function has the following attributes:

(i) it is always nonnegative; that is, it is equal to or greater than zero;

(ii) it is a rate rather than a probability;

(iii) it has no upper bound (i.e., it can assume values from zero up to infinity).

The nature of the hazard function can be constant over time (exponential model), increasing over time (increasing Weibull), decreasing over time (decreasing Weibull), or a mixture of increasing and decreasing function over time (log-normal).[338] Even though the survival function is more naturally appealing for analyzing survival data (as *S(t)* directly describes the survival experience of a study cohort); however, the hazard

[337] Ibid.
[338] Ibid.

function is of particular interest because it is the vehicle by which mathematical modeling of survival data is carried out (e.g., the Cox proportional hazards regression model).[339]

The Kaplan-Meier Method and Survival Curves

The Kaplan-Meier (KM) method is used in estimating and graphing survival curves. The estimated survival probabilities are computed using a product limit formula of the ordered survival times.[340] The KM estimator of the survival function at time t is given by the equation in Figure 3.3.

Figure 3.3: The Kaplan-Meier Estimator

$$\hat{S}(t) = \prod_{t_{(i)} \leq t} \frac{n_i - d_i}{n_i}$$

where:

$\hat{S}(t)$ = the estimated survival function;

$\prod_{t_{(i)} \leq t} \frac{n_i - d_i}{n_i}$ = product of all the estimated probabilities of surviving past time $t_{(i)}$ given the subject has made it to time $t_{(i)}$;

n_i = the number of subjects at risk at time $t_{(i)}$;

d_i = the number of observed events at time $t_{(i)}$;

339 Ibid.

340 Kleinbaum DG and Klein M, "Kaplan-Meier survival curves and the log-rank test."

$\frac{n_i - d_i}{n_i}$ = the estimated probability of surviving past time $t_{(i)}$ given the subject has made it to time $t_{(i)}$.[341]

For example, suppose we have 10 subjects in a cohort, where the first subject with survival time $t_{(1)} = 3$ is censored, but the second and third subjects at $t_{(2)} = 7$, and $t_{(3)} = 8$ had events. What is the KM estimator at t = 7, where survival time is in days?

Solution: Since both $t_{(1)}$ and $t_{(2)}$ are less than or equal to t = 7, there will be two terms in the product:

$$\hat{S}(7) = \prod_{t_{(i)} \leq 7} \frac{n_i - d_i}{n_i} = \frac{10-0}{10} \times \frac{9-1}{9} = \frac{10}{10} * \frac{8}{9} = \frac{8}{9} = \frac{8 * 100\%}{9}$$

$$= 88.9\%$$

Thus, 88.9% of the subjects (i.e., 8.89 persons out of the 10 subjects that started the cohort) survived past the 7th day.[342]

The Log-Rank Test

The log-rank test (also known as the Mantel-Cox test) is a non-parametric test that can be used in evaluating whether or not the estimates of survival function for two or more groups at each observed event time are statistically equivalent.[343] It is an appropriate statistical test for survival data that are right-skewed and censored. The test

[341] Ibid.
[342] Hersh M. *Survival Analysis*, *Statistical Methods II*. The University of Texas at Austin, Spring 2014.
[343] Kleinbaum DG and Klein M, "Kaplan-Meier survival curves and the log-rank test."

statistic has approximately a chi-square distribution with $g-1$ degrees of freedom, where *g* denotes the number of groups being compared.[344]

The Cox Proportional Hazards (PH) Model

Unlike the KM estimator and the log-rank test which cannot accommodate controls for confounding variables, the Cox proportional hazards model (or the Cox model) is a regression-type model used for comparing the survival experience of two groups while adjusting for the possible confounding and/or interaction effects of other covariates.[345] The Cox model is particularly useful because of its robustness. This implies that a reasonably good estimate of regression coefficients and hazard ratios (i.e., the hazard for one group divided by the hazard of another group) can be obtained without specifying the nature of the baseline hazard function.[346]

Apart from using it to obtain regression coefficients and relative risks (or hazard ratios), the Cox model can also be used to obtain survival curves for each treatment groups that are adjusted for the effects of covariates. These adjusted survival curves are unlike those obtained from the KM estimator survival curves which do not adjust for the effects of covariates.[347]

The Cox model (Figure 3.4) is usually written in terms of the hazard function. This model gives an expression for the hazard at time *t* for an individual with a given specification of a set of explanatory (independent) variables denoted by X_i.

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[344] Ibid.
[345] Kleinbaum DG and Klein M, "The Cox proportional hazards model and its characteristics."
[346] Ibid.
[347] Ibid.

Figure 3.4: The Cox PH Model

$$h(t, X) = h_0(t)e^{\sum_{i=1}^{p} \beta_i X_i}$$

OR

$$h(t, X) = h_0(t)exp\left[\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_p X_p\right]$$

The Cox model says that the hazard at time *t* is the product of two quantities:

$h_0(t)$ = the baseline hazard function; and

$e^{\sum_{i=1}^{p} \beta_i X_i}$ = the exponential expression *e* to the linear sum of $\beta_i X_i$, where this sum is over the p explanatory X_i variables (i.e., $X_i = X_1, X_2, X_3, \ldots X_p$); and β_i is the regression coefficient for the corresponding X_i variable (i.e., $\beta_i = \beta_1, \beta_2, \beta_3, \ldots \beta_p$).

The Hazard Ratio

The hazard ratio (HR) is a ratio of the hazard function of the active group (X_a) compared to the hazard function of the reference group (X_b). It is the unit by which the relative risks of an outcome of interest between two groups are expressed in survival analysis. It is analogous to the relative risk in multiple regression, and the odds ratio in logistic regression.[348] The estimated hazard ratio is given by the formula in Figure 3.5.

[348] Ibid.

Figure 3.5: The Hazard Ratio

$$HR = \frac{h(t, X_a)}{h(t, X_b)}$$

where:

$h(t, X_a)$ = the hazard function for the active group at time t;

$h(t, X_b)$ = the hazard function for the reference group at time t, while controlling for other explanatory variables.[349]

The Proportional Hazards Assumption

An important feature of the Cox PH model is that the hazard function is assumed to be constant over time. In other words, the survival curve of the two groups being compared should have the same shape and remain parallel over time.[350] This property is known as the proportional hazards assumption. In other not to violate the proportionality assumption therefore, the explanatory variables are assumed not to change over time (i.e., they should be time-independent). However, the Cox model can still accommodate time-dependent variables but such model will no longer satisfy the PH assumption except an interaction term is included in the model (however, the inclusion of an interaction term makes the independent contributing effects of the explanatory variables more difficult to explain).[351] It is noteworthy that although variables such as age and weight may change over time, it may be appropriate to treat such variables as time-independent variables in

[349] Ibid.
[350] Kleinbaum DG and Klein M, "Evaluating the proportional hazards assumption."
[351] Ibid.

the analysis if their effect on survival risk depends essentially on the value at only one measurement (i.e., on their baseline values).[352] In this situation, the proportional hazards assumption is not violated.

There are three general approaches for assessing the PH assumption. These include a graphical procedure, a goodness-of-fit testing procedure, and a procedure that involves the use of time-dependent covariates.[353]

The graphical approach involves either a comparison of the estimated log-log KM survivor curves over the levels of the variable being investigated (parallel curves indicate that the PH assumption is satisfied), or comparing the observed with predicted survivor curves (the observed and predicted survival curves are plotted on the same graph. If the two curves are close, then the PH assumption is reasonable). The drawback regarding the use of the graphical approach is the subjective decision regarding whether the curves are parallel. A second disadvantage is the difficulty in evaluating the PH assumption for several variables simultaneously.[354]

A second approach for assessing the PH assumption involves the goodness-of-fit tests. This approach is more appealing than the graphical approach because the chi-square statistics and the p-value computed for each variable in the model – while adjusting for the effect of other variables – can be used for making more objective decision. A large,

[352] Ibid.
[353] Ibid.
[354] Ibid.

non-significant p-value (i.e., a p-value that is greater than the nominal p-value, say p>0.01) suggests that the PH assumption is reasonable.[355]

The third approach for assessing the PH assumption involves the use of time-dependent covariates. This method involves the inclusion of an interaction term (i.e., the product) of the time-independent variable being assessed (e.g., age) and some function of time (time=survival time). A p-value obtained that is less than the p-value used in assessing statistical significance suggests that the PH assumption is not met.[356] However, addition into the regression model of any time-dependent covariate that violates the PH assumption means that the method for 'diagnosing the disease is also the cure.'[357] In other words, when a time-dependent covariate that does not satisfy the PH assumption is controlled for in a model, this means that the proportionality of hazard assumption is no longer violated for that variable.[358] The choice of which function of time to use (i.e., whether $f(t)$ equals t or $\ln t$) is not clear cut, and it is possible that different choices may result in different conclusions about whether the PH assumption is violated or not.[359] However, some researchers use the natural log of time ($\ln t$) to avoid large numerical values that may arise from multiplying the predictor variable by t rather than $\ln t$.[360]

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355 Ibid.
356 Ibid.
357 Allison PD. "Cox models with non-proportional hazards." Chap. 5 In *Survival analysis using the SAS(R) system : a practical guide*, 155-57. Cary, NC: SAS Institute Inc., 1995.
358 Kleinbaum DG and Klein M, "Evaluating the proportional hazards assumption."
359 Ibid.
360 Allison PD, "Cox models with non-proportional hazards."

3.3.3.4.2 Binary Logistic Regression

The binary logistic regression model (or the logit model) was the second statistical procedure (the first being survival analysis) that was used to analyze the retrospective cohort design. The overall direction of the association between statin therapy and incident diabetes should remain the same irrespective of the analysis method used within the retrospective cohort design. The logistic regression model was appropriate because it allowed evaluation of the effects of the primary explanatory variable (i.e., statin users vs. non-statin users, which can be binary or categorical) on the binary outcomes variable (i.e., incidence of diabetes: yes/no), while controlling for the effects of other confounding variables (which can be continuous, binary, or categorical).[361]

The logit model for the odds of having incident diabetes for any given subject is given by the following equation in Figure 3.6.[362]

Figure 3.6: The Logistic Regression Model

$$log\left(\frac{P}{1-P}\right) = \beta_0 + \sum_{i=1}^{K} \beta_i X_i$$

$$log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_K X_K$$

[361] Hosmer DW, Lemeshow S, and Sturdivant RX. "Introduction to the logistic regression model." Chap. 1 In *Applied Logistic Regression*, 1-8. Hoboken: Wiley, 2013.
[362] Ibid.

$$\frac{P}{1-P} = e^{\beta_0+\beta_1 X_1+\beta_2 X_2+\beta_3 X_3+\cdots+\beta_K X_K}$$

where:

$\frac{P}{1-P}$ = the odds of incident diabetes;

P = the probability of having incident diabetes;

$1 - P$ = the probability of NOT having incident diabetes;

β_0 = intercept;

$\sum_{i=1}^{K} \beta_i X_i$ = product of the regression coefficient β_i and the corresponding explanatory variable X_i, summed over values of i ranging from 1 to K.[363]

3.3.3.4.3 The Odds Ratio

The odds ratio (OR) is a ratio of the odds of the event happening in the active group compared to the odds of the event happening in the reference group. It is the unit by which the relative risks of an outcome of interest between two groups are expressed in logistic regression analysis.[364]

For example, assuming the exposure variable (coded as 1=statin users and 0=non-statin users) in Figure 3.6 is represented by the explanatory variable X_1, then the odds ratio (OR) comparing the odds of incident diabetes among statin users relative to the odds of incident diabetes among non-statin users (assuming no interaction effects, and controlling for other explanatory variables $X_2 - X_K$) is given by:

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[363] Ibid.

[364] Kleinbaum DG, and Klein M. "Introduction to logistic regression." Chap. 1 In *Logistic regression: A self-learning text*, 1-27. New York, NY: Springer, 2010.

$$OR = e^{\beta_1}$$

where:

e^{β_1}= exponentiation of β_1 (the regression coefficient of the exposure variable X_1) to base e.[365]

For example, if the OR = 2.5 at a significance level of $p<0.05$, this is interpreted as: the odds of incident diabetes among statin users is 2.5 times the odds of incident diabetes among non-statin users, controlling for other variables. In simple terms, it means statin therapy is significantly associated with incident diabetes.

3.4 DATA SOURCE

This retrospective claims analysis utilized data from the *Truven Health MarketScan® Commercial Claims & Encounters Database* (also known as the *Thomson Reuters MarketScan® Commercial Claims and Encounters Database, or the MarketScan® Database*) for the period of 2003 to 2004.[366] The data were provided as part of the *Thomson Reuters MarketScan* Dissertation Support Program.

The *MarketScan Commercial Claims and Encounters Database* consists of employer- and health plan-sourced data containing medical and prescription data for several million individuals annually, including employees, their spouses, and dependents who are covered by employer-sponsored private health insurance. These private health plans include fee-for-service (FFS) plans, preferred provider organizations (PPO),

[365] Ibid.
[366] Thomson Reuters (Healthcare) Inc. 2011 *Thomson Reuters MarketScan* publication and trademark guidelines. 2011:1-2.

exclusive provider organizations (EPO), point of service plans (POS), indemnity plans, and health maintenance organizations (HMO).[367]

The *MarketScan* claims database is one of the largest proprietary databases in the US with over 170 million unique patients since 1995 and with 56 million covered lives in the most recent full data year.[368] One limitation of the *MarketScan* database is that it is a convenience sample; however, it has a large enough sample size that allows for the creation of a nationally representative data sample of Americans with employer-sponsored health insurance in all 50 states of the US and Puerto Rico.[369] Health care claims from the *MarketScan Database* are sourced mainly from large employers. Medium and small firms are underrepresented.[370]

The 2003 and 2004 *MarketScan* data used for this project had a combined enrollment of over 11 million unique individuals who are 20 – 64 years old. Table 3.1 summarizes the annual enrollment demographics (e.g., age group, gender, region, and health plan) of the 2003 and 2004 *MarketScan Commercial Claims and Encounters Database*.

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[367] Hansen LG, and Chang S. White Paper. Health research data for the real world: The MarketScan Databases. 2012:1-19.
[368] Ibid.
[369] Ibid.
[370] Ibid.

Table 3.1: Demographic Characteristics of the *MarketScan* Data		
DEMOGRAPHICS	**2003**	**2004**
Age Group	**Percent**	**Percent**
0 – 17	25.63	25.59
18 – 34	22.88	21.95
35 – 44	16.74	16.29
45 – 54	18.90	19.34
55 – 64	15.78	16.84
65 and older	0.08	-
Gender		
Male	47.39	47.49
Female	52.61	52.51
Region		
Northeast	11.89	11.20
North Central	26.99	26.63
South	39.49	41.59
West	20.38	19.15
Unknown	1.25	1.43
Health Plan		
Employer	100.00	100.00

Source: Truven Health Analytics MARKETSCAN® Commercial Claims & Encounters Enrollment Annual Summary – 2003 & 2004 Version 5.0 Data Quality Reports.

3.4.1 Data Quality Control

Data quality controls to ensure reasonableness against norms are routinely conducted during the *MarketScan Database* creation.[371] Examples of reasonableness checks include diagnosis against age, diagnosis against sex, and charges against payment. Validity checks are conducted for selected fields, including diagnosis codes, procedure codes, service dates, sex, and age, to compare recorded values to lists of possible valid values for those fields.[372] Additional enhancement to the data control include comparing

[371] Truven Health Analytics. Truven Health MarketScan Research Databases: Commercial Claims and Encounters Medicare Supplemental data year 2011 edition. 2012:21-23.
[372] Ibid.

diagnosis and procedure codes to codes that were in effect at that time and editing them if necessary, and creating a common synthetic patient identifier so that patients can be tracked over years and across different files while ensuring patient confidentiality.[373]

3.4.2 Data Elements

The *MarketScan® Database* consists of demographic, medical, health plans, financial, drug, and enrollment information for employees, their spouses and dependents who are covered by employer-sponsored private health insurance.[374] Medical claims are linked to outpatient prescription drug claims and person-level enrollment information through a unique enrollee identifier across files and across years of data.[375]

The data elements extracted from the *MarketScan Database* included demographic information (patient de-identified unique ID, age, and gender); inpatient and out-patient medical information (diagnosis codes, major diagnostic category, principal procedure code, secondary diagnosis codes [up to 14], secondary procedure codes [up to 14], diagnosis-related group); drug information (national drug codes, therapeutic class, days of medication supplied, prescription refill number, and therapeutic group number); and enrollment information (date enrollment start, date enrollment end, enrollment indicator month 1 – 12, enrollment months, and member days month 1 – 12). A full description of the *MarketScan* data elements is presented in Table 3.2.

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[373] Ibid.
[374] Hansen LG and Chang S, "White Paper. Health research data for the real world: The MarketScan Databases."
[375] Ibid.

Table 3.2: Description of the *MarketScan* Data Elements				
Variable	**Type**	**Long Name**	**Description**	**Valid Content**
Outpatient Prescription Drugs File				
AGE[a]	Num	Age of Patient	Patient age in years at the time of service	Each character = 0-9
DAYSUPP	Num	Days Supply	The number of days of drug therapy covered by this prescription	Each character = 0-9
DOBYR[a]	Num	Patient Birth Year	Year of patient birth	CCYY[c]
ENROLID[a]	Num	Enrollee ID	A unique 3-11 digit number identifying each enrollee in the data file	Each character = 0-9
NDCNUM	Char	National Drug Code	The full 11 digits of FDA registered number	Each character = 0-9; FDA's 10-digit NDC codes zero- filled to 11 characters
REFILL	Num	Refill Number	A number indicating whether this is the original prescription (0), or the refill number (1, 2, 3, etc.)	Each character = 0-9
SEX[a]	Char	Gender of Patient	Gender of the patient	1=Male, 2=Female
SVCDATE[b]	Num	Date Service Incurred	Date of inpatient or outpatient service or date prescription was filled	mmddyy10.[d]
THERCLS	Num	Therapeutic Class	A 3-digit code that indicates the therapeutic/pharmacologic category of the drug product	Each character = 0-9
THERGRP	Char	Therapeutic Group	A 2-digit code that further aggregates the THERCLS values	Each character = 0-9
WGTKEY[a]	Num	*MarketScan* National Weight Link	An integer key linking to national weight values for the record	1-72, Missing

Table 3.2: Description of the *MarketScan* Data Elements (cont'd)				
Variable	**Type**	**Long Name**	**Description**	**Valid Content**
YEAR[a]	Num	Date Year Incurred	The calendar year during which the service was rendered, the admission began, or the population was eligible	CCYY
Enrollment Information File				
DTEND	Num	Date Enrollment End	End date of continuous enrollment period	mmddyy10.
DTSTART	Num	Date Enrollment Start	Start date of continuous enrollment period	mmddyy10.
ENRIND1 through ENRIND12	Num	Enrollment Indicator Month 1 through Enrollment Indicator Month 12	A flag which indicates that an individual was enrolled in the specified month	0=Not enrolled 1=Enrolled
ENRMON	Num	Enrollment Months	Total number of months during the year in which an individual was enrolled	1-12
MEMDAY1 through MEMDAY12	Num	Member Days Month 1 through Member Days Month 12	The number of days an individual was enrolled during the specified month	Each character = 0-9
MEMDAYS	Num	Member Days	The number of member days an enrollee was enrolled	Each character = 0-9

Table 3.2: Description of the *MarketScan* Data Elements (cont'd)				
Variable	**Type**	**Long Name**	**Description**	**Valid Content**
Inpatient Services and Outpatient Services Files				
DX1 through DX15	Char	Diagnosis 1 through Diagnosis 15	The principal diagnosis and up to 14 secondary diagnosis codes as recorded on the service records	
PDX	Char	Principal Diagnosis	Principal diagnosis explains the main reason for an admission; usually the discharge diagnosis	
PPROC	Char	Principal Procedure	Principal procedure is the procedure performed during an admission that had the greatest influence on which DRG was assigned to the admission	
PROC1 through PROC15	Char	Procedure 1 through Procedure 15	The principal procedure (PROC1) and up to 14 other procedures as recorded chronologically on the service record.	
TSVCDAT	Num	Date Service Ending	The end date for a service	mmddyy10.

Source: Truven Health Analytics. *2011 Truven Health MarketScan Commercial Claims and Encounters Medicare Supplementation and Coordination of Benefit data dictionary.* Ann Arbor, MI. 2012.

Abbreviations: Num, Numeric; Char, Character; FDA, Food and Drug Administration; DRG, Diagnosis Related Group.

[a]These variables are present within the Outpatient Prescription Drug file, the Enrollment Information file, and the Outpatient Services and Inpatient Services files.

[b]Variable absent in the Enrollment Information file, but present in the Outpatient Prescription Drug file and the Outpatient Services and Inpatient Services files.

[c]A date format showing a two-digit century and year (e.g., 2004; where CC is 20 and YY is 04).

[d]mmddyy10. is a SAS date format. For example, December 23, 2003 will be displayed as 12/23/2003 using this format.

3.4.3 Diagnosis and Procedure Codes in the *MarketScan* Data

Diagnosis Codes

The diagnosis codes in *MarketScan* data used the ICD-9-CM classification system.[376] The diagnosis codes are three to five characters in length (Table 3.3). The first character was alphanumeric (0 – 9, E or V), while characters two to five were numeric or blank. In *MarketScan* data, the decimal point was implied between the third and fourth digit of the code.

Table 3.3: ICD-9-CM Diagnosis Codes in *MarketScan* Data

ICD-9-CM	***MarketScan* Data Value**
390	390 (followed by 2 spaces)
012.1	0121 (followed by 1 space)
223.89	22389

Source: Truven Health Analytics. *Truven Health MarketScan Research Databases: Commercial Claims and Encounters Medicare Supplemental data year 2011 edition.* Ann Arbor, MI. 2012:21-23.

[376] Truven Health Analytics, "Truven Health MarketScan Research Databases: Commercial Claims and Encounters Medicare Supplemental data year 2011 edition."

Procedure Codes

The ICD-9-CM procedure codes (found on hospital claims) are three to four digits in length and are all numeric (Table 3.4). There was an implied decimal between the second and third digits in the *MarketScan* data value. The ICD-9-CM procedure codes used in the *MarketScan* data are five characters in length.

Table 3.4: ICD-9-CM Procedure Codes in *MarketScan* Data

ICD-9-CM	***MarketScan* Data Value**
13.9	139 (followed by 2 spaces)
13.19	1319 (followed by 1 space)

Source: Truven Health Analytics. *Truven Health MarketScan Research Databases: Commercial Claims and Encounters Medicare Supplemental data year 2011 edition.* Ann Arbor, MI. 2012:21-23.

3.4.4 The National Drug Code in the *MarketScan* Data

The FDA's National Drug Code is a unique 10-digit, 3-segment code (with the 4-4-2, 5-3-2, or the 5-4-1 configuration) that serves as a universal product identifier for drugs.[377] The first segment (assigned by the FDA), is called the labeler code. A labeler is any firm that manufactures (including repackers or relabelers), or distributes (under its own name) the drug. The second segment, called the product code, identifies the strength, dosage form, and formulation of a drug. The third segment, called the package code, identifies the package sizes and types. Both the product code and the package code are assigned by the drug firm.[378]

[377] U.S. Food and Drug Administration. National Drug Code directory. 2014; Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm. Accessed July 1, 2014.
[378] Ibid.

The NDC number within the *MarketScan* data was an 11-digit, 5-4-2 configuration code obtained by padding with zeroes, in the appropriate places, the FDA's 10-digit NDC codes (Table 3.5).[379] The NDC codes used to identify all drugs in this study were obtained from the already standardized, 11-digit, 5-4-2 configured FDA's NDC codes published by the RED BOOK Online®.[380] The RED BOOK Online® (and Micromedex® 2.0 through which it was accessed) are brand products of Truven Health Analytics, the owner of the *MarketScan* data.

Table 3.5: NDC Codes in the *MarketScan* Data

FDA's NDC Configuration	***MarketScan* Data's 5-4-2 Format**
4-4-2: XXXX-XXXX-XX	**0**XXXX-XXXX-XX
5-3-2: XXXXX-XXX-XX	XXXXX-**0**XXX-XX
5-4-1: XXXXX-XXXX-X	XXXXX-XXXX-**0**X

Source: Truven Health Analytics. *Truven Health MarketScan Research Databases: Commercial Claims and Encounters Medicare Supplemental data year 2011 edition.* Ann Arbor, MI. 2012:61.

379 Truven Health Analytics, "Truven Health MarketScan Research Databases: Commercial Claims and Encounters Medicare Supplemental data year 2011 edition."

380 Truven Health Analytics. RED BOOK online search. 2014; Available at: http://www.micromedexsolutions.com.ezproxy.lib.utexas.edu/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/620D43/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/E495C2/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/redbook.FindRedBook. Accessed July 1, 2014.

3.5 SAMPLE SIZE CALCULATION

The sample size required for the retrospective cohort design was determined from five parameters. These include:

- The tolerable type I error rate or alpha: this two-tailed alpha was be set at 0.01. Sample size sensitivities was conducted for alpha=0.05.
- The tolerable type II error rate (β): this was conventionally set at 0.2 to result in a minimum level of power of 80% (i.e., 1-β) in order to be able to detect differences between two groups if one truly existed.
- The minimum effect size (i.e., the relative risk of disease in the exposed population): based on results from five retrospective cohort studies that evaluated the association between statin therapy and incidence of diabetes, the average relative risk of diabetes in patients exposed to different statin types compared to non-users of statins was 1.17 (note: average was for those with RR > 1, see Table 2.25).[381] Similarly, the average relative risk of diabetes in patients exposed to statins as a class compared to unexposed subjects was 1.17 in two retrospective cohort studies.[382] The average relative risk obtained from two prospective cohort studies that examined the

[381] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."
[382] Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

association between statin use and incidence of diabetes was 1.26.[383] A relative risk of 1.25 was assumed for this study, with sample size sensitivities calculated for relative risks of 1.50 and 1.75.

- The expected incidence of the disease in the unexposed population: the 2011 age-adjusted incidence of diabetes among US adults aged 18 – 76 years was 7.6 per 1,000 persons (or 0.76% or 0.0076). This incidence value was used because the *MarketScan Database* is assumed to be fairly representative of the entire US population.[384] Sample size sensitivity analyses were conducted for incidence values of 0.005 and 0.01.
- The number of the unexposed subjects to be included in the study for each exposed subjects: this was set at a one-to-one ratio (1:1).

An estimate of the sample size required for the retrospective cohort design was estimated from an online calculator for calculating sample size for a cohort study.[385] Sample size estimates from this online tool yielded approximately the same values when

[383] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."
[384] Hansen LG and Chang S, "White Paper. Health research data for the real world: The MarketScan Databases."
[385] Sergeant E. Epitools epidemiological calculators: sample size for a cohort study. 2014; Available at: http://epitools.ausvet.com.au/content.php?page=cohortSS. Accessed 12/10, 2014.

validated against estimates from the Strom and Kimmel sample size table [386] which used the Schlesselman formula (Figure 3.7) for calculating sample sizes in cohort studies.[387]

Figure 3.7: Sample Size Formula for Cohort Design

$$\boldsymbol{N = \frac{1}{[p(1-R)]^2}\left[Z_{1-\alpha/2}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{\left(pR(1-Rp) + \frac{p(1-p)}{K}\right)}\right]^2}$$

where:

N = Number of sample size required for the exposed group;

p = Incidence of diabetes within the unexposed group ($7.6/1000 = 0.0076$);

R = The minimum relative risk of diabetes among the exposed compared to the unexposed (1.25; sample size sensitivities was calculated for $R = 1.50$ and $R = 1.75$).

α = Type I error rate (0.01; sample size sensitivities was calculated for $\alpha = 0.05$);

β = Type II error rate (0.2);

$Z_{1-\alpha/2}$ and $Z_{1-\beta}$ = unit normal deviates corresponding to α and β (Note: α was divided by 2 because two-tailed tests were assumed; β or power is typically one-tailed; $Z_{1-\alpha/2} = Z_{0.975} = 1.96$; while $Z_{1-\beta} = Z_{0.8} = 0.84$).

K = ratio of number of unexposed subjects to the number of exposed subjects ($1/1=1$);

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[387] Schlesselman JJ. Sample size requirements in cohort and case-control studies of disease. Am J Epidemiol. 1974;99(6):381-4.

$$U = \frac{Kp+pR}{K+1}.$$

Given the above parameters, and using the online sample size tool (sample size values cannot be estimated for relative risk < 1 using this online tool), the number of subjects required for the exposed group (i.e., statin users) was **54,843.** An equal number was required for the unexposed group (i.e., non-statin users). Thus, the total sample size required for the retrospective cohort design was **109,686**. Table 3.6 shows an estimation of the sample sizes required when the values of α (type I error), p (incidence in the unexposed group) and R (relative risk to be detected) are varied.

Table 3.6: Sample Sizes for Cohort Studies[a]

α	Incidence in the unexposed group	Relative risk to be detected		
		1.25	**1.50**	**1.75**
0.01	**0.005**	83,610	23,207	11,336
	0.0076	**54,843**	15,216	7,429
	0.01	41,566	11,528	5,626
0.05	**0.005**	56,191	15,596	7,618
	0.0076	36,858	10,226	4,993
	0.01	27,935	7,747	3,781

Source: Sergeant E. Epitools epidemiological calculators: sample size for a cohort study. 2014

$[\beta = 0.2\ (80\%\ Power), exposed{:}\ unexposed\ ratio = 1{:}\ 1\ ]$

[a]The sample size shown is the number needed among the exposed group.

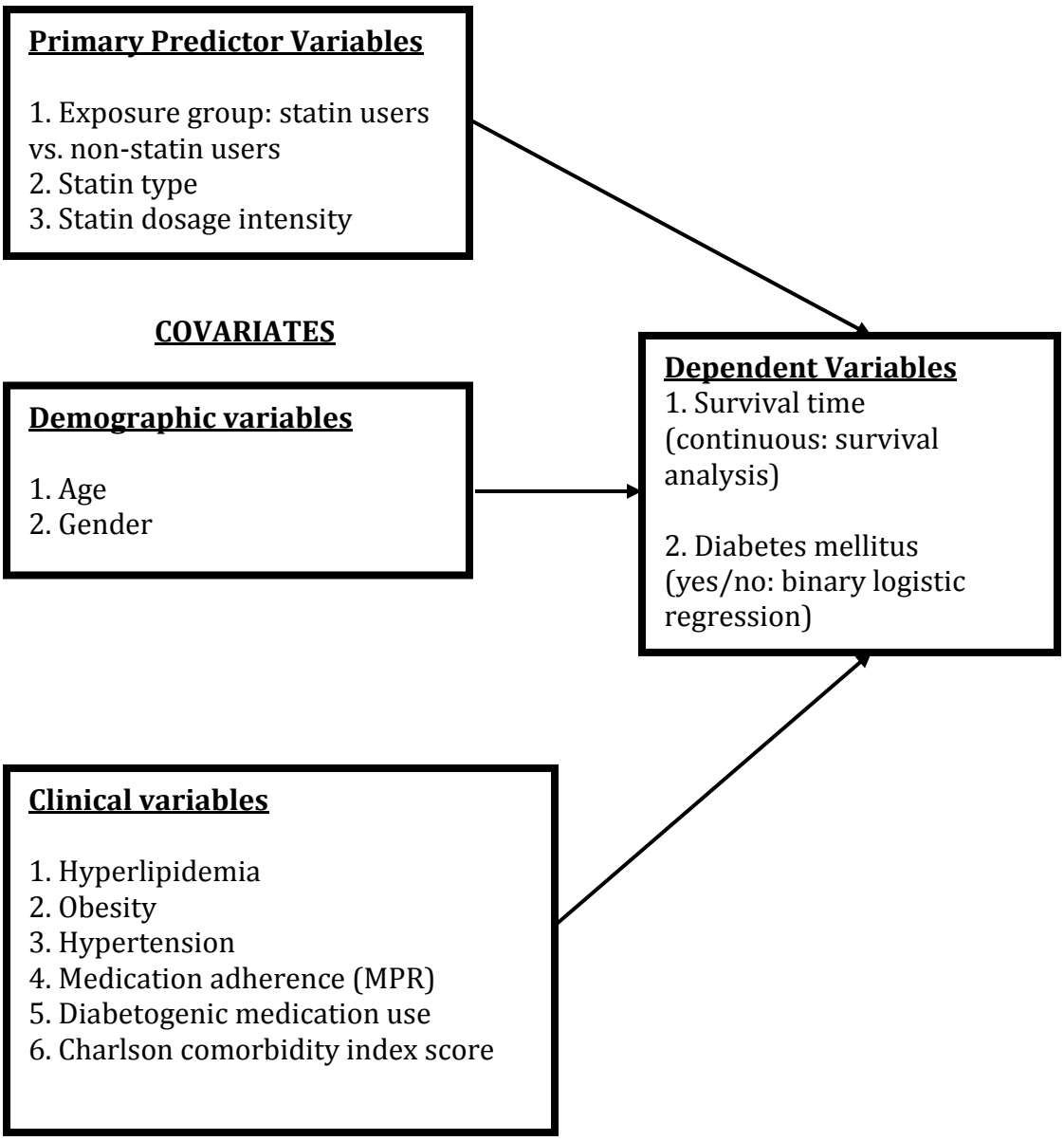
3.6 STUDY VARIABLES

This section describes all the relevant available study variables – both the primary predictor variable of interest (exposure group, statin types, and statin dosage intensity), and the clinical covariates that was controlled for in the investigation of the association between statin exposure and the occurrence of incident diabetes.

3.6.1 Study Model

Figure 3.8 illustrates the study model (containing the dependent and independent variables) for the retrospective cohort design.

Figure 3.8: Study Model for the Retrospective Cohort Design



3.6.2 Dependent Variables

I. Survival Time

Survival time was defined as the duration of time (in months) from when a subject was first exposed to the index medication to the first date of diabetes diagnosis.

II. Incidence of Diabetes

The occurrence of diabetes incidence was defined as the first date a subject was diagnosed with a new case of diabetes after exposure to the index medication. Incident diabetes was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes 250.xx (diabetes mellitus). To ensure that subjects with only incident cases of diabetes were included in the cohort, the retrospective cohort design required that subjects do not have a diagnosis of diabetes in the pre-index period (a period of six months before the index date). In other words, subjects with previous cases of diabetes (or prevalent cases of diabetes) were excluded from the cohorts.

3.6.3 Independent Variables

In order to have a high confidence of inferring or not inferring that statin therapy was associated with new diabetes mellitus, it was important that certain confounding variables be controlled for in the statistical analyses. Confounding variables that were controlled for included demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, statin medication adherence, diabetogenic medications, and CCI score).

The operational definitions of the available independent variables are discussed in the following section.

3.6.3.1 Primary Predictor Variables

The primary predictor variables included exposure group, statin types, and statin dosage intensity.

I. Exposure Group

Subjects who were initially free of diabetes were divided into two exposure group cohorts: statin users and non-statin users.

(a) Statin Users

Statin users were defined as those that had at least one prescription for any of the statins available within the 2003-2004 *MarketScan Database*.[388] These statins included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Pitavastatin was not included because it was approved in 2009, five years after the study endpoint.

(b) Non-Statin Users

Non-statin users were defined as subjects who did not receive prescription for any statin, including statins that existed in any combined dosage form with other drugs throughout the observation period. This definition has been used in previous

[388] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

observational studies that examined the association between statin therapy and incidence of diabetes mellitus.[389]

II. Statin Type

In addition to examining the overall association of statins (as a class) and incidence of diabetes, users of each statin type were also compared to non-statin users in order to determine their relative risk of incident diabetes. For the purpose of this study, six statin types were considered. They included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

III. Statin Dosage Intensity

A meta-analysis of five RCTs suggested that intensive-dose statin therapy was associated with higher risk of incident diabetes compared to moderate-dose statin therapy.[390] Statin doses were dichotomized into: 1 = intensive dose and 0 = moderate dose (reference category). These doses are defined in Table 3.7 by type of statin.

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[389] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."; Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

[390] Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

Table 3.7: Moderate vs. Intensive Statin Dosages		
Statin	**Moderate Dose (mg)**	**Intensive Dose (mg)**
Atorvastatin	10, 20	40, 80
Fluvastatin	20, 40, 80	-
Pravastatin	10, 20, 40, 80	-
Lovastatin	10, 20, 40, 60	-
Rosuvastatin	5, 10	20, 40
Simvastatin	5, 10, 20, 40	80

Source: Texas Diabetes Council. Lipid algorithm for type 1 and type 2 diabetes mellitus in adults; 2011. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA.* 2011;305(24):2556-2564.

3.6.3.2 Demographic Variables

I. Age

Age is an independent risk factor for diabetes mellitus.[391] Age is a continuous variable that was defined as the age (in years) when subjects received their first index medication.

II. Gender

Among the US adult population aged 20 years or older, the prevalence of diabetes was higher among males compared to females.[392] Gender is a dichotomous variable that was coded as 1 = male and 0 = female (reference category).

[391] American Diabetes Association, "Standards of medical care in diabetes--2014."
[392] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."

3.6.3.3 Clinical Covariates

I. Hyperlipidemia

Due to the problem of confounding by indication (i.e., the possibility that hyperlipidemia – the indication for which statins are used – was responsible for the association between statin therapy and incident diabetes, and not the statin itself), it was necessary to control for hyperlipidemia diagnosis. Hyperlipidemia is a risk factor for metabolic syndrome and cardiovascular diseases,[393] which are in turn risk factors for diabetes mellitus.[394] The hyperlipidemia (or hyperlipidemia diagnosis) variable was identified by ICD-9-CM codes 272.0 (pure hypercholesterolemia: high TC), 272.1 (pure hypertriglyceridemia: high TG), 272.2 (mixed hyperlipidemia: high LDL-C, high TG, and low HDL-C), and 272.4 (other and unspecified hyperlipidemia).[395] Hyperlipidemia is a dichotomous variable that was coded as 1 = hyperlipidemia present, and 0 = hyperlipidemia absent (reference category).

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[393] Wilson PW et al., "Prediction of coronary heart disease using risk factor categories."; "The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease."; "Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering."

[394] Carr MC, and Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: Importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. J Clin Endocrinol Metab. 2004;89(6):2601-07.

[395] ICD9Data.com: disorders of lipoid metabolism. Available at: http://www.icd9data.com/2014/Volume1/240-279/270-279/272/default.htm. Accessed June 17, 2014.

II. Obesity

The epidemic of gestational and type 2 diabetes in the US has been attributed to increasing rates of overweight and obesity.[396] Because obesity increases insulin resistance, overweight and obese individuals are therefore especially at greater risk for diabetes.[397] The obesity (or obesity diagnosis) variable was identified using ICD-9-CM codes 278.00 (obesity, unspecified) and 278.01 (morbid obesity).[398] Obesity is a dichotomous variable that was coded as 1 = obesity present, and 0 = obesity absent (reference category).

III. Hypertension

Hypertension (or high blood pressure) is an independent risk factor for diabetes mellitus.[399] The hypertension (or hypertension diagnosis) variable was identified using ICD-9-CM codes 401.0 (malignant essential hypertension), 401.1 (benign essential hypertension), and 401.9 (unspecified essential hypertension). Hypertension is a dichotomous variable that was coded as 1 = hypertension present, and 0 = hypertension absent (reference category).

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396 Kirkman MS et al., "Diabetes in older adults."; Lawrence JM et al., "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005."

397 Norris SL et al., "Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review."

398 "ICD9Data.com: disorders of lipoid metabolism".

399 American Diabetes Association, "Standards of medical care in diabetes--2014."

IV. Medication Adherence

Medication adherence (a proxy for estimating drug exposure and compliance with medication dosage regimen) was estimated using the medication possession ratio (MPR).[400] MPR as defined as the total number of days of medication supplied during a defined period of time divided by the length of therapy.[401] The length of therapy (the denominator of MPR) was defined as the number of days elapsed between the first and the last prescription fill dates.[402] With the denominator defined this way, the numerator is now redefined as the total number of days of medication supplied before the last fill date (the number of days supply for the last prescription is not added to the numerator).[403]

MPR is a continuous variable that was computed by the formula in Figure 3.9. MPR values greater than 1 (or 100%) were truncated to 100%.

Figure 3.9: Medication Possession Ratio (MPR)

$$MPR = \frac{Sum\ of\ number\ of\ days\ of\ Rx\ supplied\ (minus\ last\ Rx\ days\ supply)}{Sum\ of\ days\ between\ first\ Rx\ and\ last\ Rx\ fill\ dates}$$

[400] Fairman KA, and Motheral B. Evaluating medication adherence: which measure is right for your program. J Manag Care Pharm. 2000;6(6):502.
[401] Richhariya A. "Impact of Medicare Part D on adherence and persistence to statin medications for Texas dual-eligible beneficiaries." Thesis, The University of Texas at Austin, 2010.
[402] Ibid.
[403] Ibid.

V. Diabetogenic Medication Use

In assessing the association between statin use and incidence of diabetes, it was important to account for the potential confounding effect of certain drugs and agents that have been shown to independently increase the risk of diabetes. These drugs included thiazide diuretics,[404] β-blockers,[405] antipsychotic agents,[406] antidepressants,[407] glucocorticoids (especially prednisolone and dexamethasone),[408] and immunosuppressive agents (especially tacrolimus and cyclosporine).[409]

The diabetogenic medication variable is a continuous variable that was obtained by summing the number of prescriptions for all diabetogenic medications filled during the observation period for any of the above diabetogenic medications. A prescription fill was defined as a 30-day supply of the diabetogenic medication.

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[404] Zillich AJ et al., "Thiazide diuretics, potassium, and the development of diabetes: A quantitative review."; Elliott WJ and Meyer PM, "Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis."

[405] Kuti EL et al., "The development of new-onset type 2 diabetes associated with choosing a calcium channel blocker compared to a diuretic or beta-blocker."; Bangalore S et al., "A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus."

[406] Holt RI and Peveler RC, "Association between antipsychotic drugs and diabetes."

[407] Khoza S et al., "Use of antidepressants and the risk of type 2 diabetes mellitus: a nested case-control study."

[408] Kwon S and Hermayer KL, "Glucocorticoid-induced hyperglycemia."

[409] Penfornis A and Kury-Paulin S, "Immunosuppressive drug-induced diabetes."; Vincenti F et al., "Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus."

VI. Charlson Comorbidity Index Score

Comorbidity is the co-occurrence of two or more disease conditions in a patient. Because the epidemiological design (retrospective cohort) used for this study does not involve randomization of subjects into groups, it was necessary to control for the baseline clinical conditions between the exposed and unexposed groups. Failure to control for baseline comorbid conditions may confound the relationship between the exposure of interest (statins) and occurrence of incident diabetes.

The CCI is a tool originally developed by Mary E. Charlson, MD to estimate the prognostic impact or risk of mortality associated with two or more comorbid conditions in patients.[410] The CCI is a weighted index (higher weight is assigned to more severe condition) that was calculated by summing the weights (i.e., 1, 2, 3, or 6) assigned to a set of diagnostic conditions and/or procedures (identified using the ICD-9-CM diagnostic and procedure codes) that were present at or prior to the start of the index medication use. For example, a patient with comorbid conditions of congestive heart failure (1), ulcer (1), leukemia (2), and liver disease (3) had a CCI score of 7.

The Dartmouth-Manitoba adaptation of the CCI (Table 3.8) was used for this study.[411] It was preferred over other CCI variants, such as the Deyo[412] and the

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[410] Charlson ME, Pompei P, Ales KL, and MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
[411] Romano PS, Roos LL, and Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993;46(10):1075-9; discussion 81-90.
[412] Deyo RA, Cherkin DC, and Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Ibid.1992;45(6):613-9.

D'Hoore,[413] because it incorporated ICD-9-CM procedure codes in addition to its more comprehensive ICD-9-CM diagnostic codes.

[413] D'Hoore W, Bouckaert A, and Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. Ibid.1996;49(12):1429-33.

Table 3.8: The Dartmouth-Manitoba Adaptation of the Charlson Comorbidity Index Diagnostic Categories and ICD-9-CM Codes		
Clinical Conditions	**Weights**	**Dartmouth-Manitoba ICD-9-CM codes**
Myocardial infarction	1	410.xx, 412
Congestive heart failure	1	402.01, 402.11, 402.91, 425.x, 428.x, 429.3
Peripheral vascular disease	1	440.x, 441.x, 442.x, 443.1 – 443.9, 447.1, 785.4, 38.13 – 38.14(P), 38.16(P), 38.18(P), 38.33 – 38.34(P), 38.36(P), 38.38(P), 38.43 – 38.44(P), 38.46(P), 38.48(P), 39.22 – 39.26(P), 39.29(P)#
Cerebrovascular disease	1	362.34, 430 – 436, 437 – 437.1, 437.9, 438, 781.4, 784.3, 997.0, 38.12(P), 38.42(P)
Dementia	1	290.x, 331 – 331.2
Chronic pulmonary disease	1	415.0, 416.8 – 416.9, 491.x – 494, 496
Rheumatologic disease	1	710.x, 714.x
Peptic ulcer disease	1	531.xx – 534.xx
Mild liver disease	1	571.2, 571.5 – 571.6, 571.8 – 571.9
Hemiplegia or Paraplegia	2	342.x, 344.x

Table 3.8: The Dartmouth-Manitoba Adaptation of the Charlson Comorbidity Index Diagnostic Categories and ICD-9-CM Codes (cont'd)		
Clinical Conditions	**Weights**	**Dartmouth-Manitoba ICD-9-CM codes**
Renal disease	2	585 – 586, V42.0, V45.1, V56.x*, 39.27(P), 39.42(P), 39.93 – 39.95(P), 54.98(P)
Any malignancy Lymphoma Leukemia	2	140.x – 171.x, 174.x – 195.x, 200.xx – 208.x, 273.0, 273.3, V10.46, 60.5(P), 62.4 – 62.41(P)
Moderate or severe liver disease	3	572.2 – 572.4, 456.0 – 456.2x, 39.1(P), 42.91(P)^
Metastatic solid tumor	6	196.x – 199.x^
AIDS	6	042.x – 044.x

Source: Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol.* 1993;46(10):1075-1079.

#ICD-9-CM codes with (P) following them describes procedures rather than diagnoses (Vol. III).

*ICD-9-CM codes with a 'V' before them are classified under the "Supplementary Classification of Factors Influencing Health Status and Contact with Health Services" of the ICD-9-CM diagnostic categories.

^These comorbidities take precedence over less severe comorbidities involving the same organ system.

Table 3.9 summarizes the study variables (both dependent and independent variables) for the retrospective cohort design, while Table 3.10 summarizes the operational definitions of all study variables.

Table 3.9: Summary of Study Variables in the Retrospective Cohort Design	
Dependent variables	**Independent variables**
1. Survival time 2. Incidence of diabetes	*Primary predictor variables:* 1. Exposure group (statin users vs. non-statin users) 2. Statin type (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) 3. Statin dosage intensity (intensive-dose vs. moderate-dose) *Demographic variables:* 1. Age 2. Gender *Clinical covariates:* 1. Hyperlipidemia 2. Obesity 3. Hypertension 4. Medication adherence (MPR) 5. Diabetogenic medications 6. CCI score

Table 3.10: Summary of Operational Definitions of Study Variables		
	OPERATIONAL DEFINITION	**MEASUREMENT LEVEL**
DEPENDENT VARIABLES		
Survival time (or time to occurrence of diabetes)	The period (in months) between the first date of the index medication and the diagnosis of diabetes, or the period between the index date and the end of study period (if there was no occurrence of diabetes)	Continuous
Incidence of diabetes	A diagnosis of diabetes after exposure to the index medication. Identified using ICD-9-CM codes 250.xx 1=diagnosed with diabetes 0=not diagnosed with diabetes	Dichotomous
INDEPENDENT VARIABLES		
Exposure group	The nature of drug a subject was exposed to at index date: 1=Exposed to statin 0=Not exposed to statin (reference)	Dichotomous
Statin type	The type of statin a subject was exposed to at index: 1=Atorvastatin 2=Fluvastatin 3=Lovastatin 4=Pravastatin 5=Rosuvastatin 6=Simvastatin	Nominal
Statin dosage intensity	Intensiveness of the statin therapy received during the observation period: 1= intensive-dose statin (received an intensive-dose statin at any time during the observation period) 0=moderate-dose statin (reference: received a moderate-dose statin throughout the observation period)	Dichotomous

Table 3.10: Summary of Operational Definitions of Study Variables (cont'd)		
Age	Age of each subject (in years) at the index date	Continuous
Gender	Gender of subjects at index date: 1=Male 0=Female (reference)	Dichotomous
Hyperlipidemia	Presence or absence of a hyperlipidemia diagnosis at or before index: 1=present 0=absent (reference)	Dichotomous
Obesity	Presence or absence of an obesity diagnosis at or before index: 1=present 0=absent (reference)	Dichotomous
Hypertension	Presence or absence of a hypertension diagnosis at or before index: 1=present 0=absent (reference)	Dichotomous
Medication adherence	Estimated using the medication possession ratio (MPR) defined as: $\frac{\textbf{\textit{Sum of number of days of Rx supplied (minus last Rx days supply)}}}{\textbf{\textit{Sum of days between first Rx and last Rx fill dates}}}$	Continuous
Diabetogenic medication use[a]	Sum of all/each diabetogenic medication prescriptions filled at pre- and post-index: 1 prescription fill= 30-day supply of a diabetogenic medication filled during the observation period (observation period was defined as the period between the start of the pre-index period and the cohort exit)	continuous
CCI score	The sum of weights related to each comorbid condition before or at index	Continuous

[a]Diabetogenic medication variables included thiazide diuretics, β-blockers, antipsychotics, antidepressants, immunosuppressants and glucocorticoids.

3.7 DATA ANALYSIS PROCEDURES

Data manipulation and analyses was performed using SAS® for Windows® version 9.3 (SAS Institute, Cary, NC) and IBM SPSS Statistics Version 21 (SPSS Inc, Chicago, IL).

Preliminary analysis (using the minimum and maximum function) was used to identify problematic observations (i.e., outliers) that may impact the study results. In addition, appropriate preliminary analyses (e.g., normality, chi-square assumptions, multicollinearity, and proportionality of hazards regression) were performed to assess the validity of assumptions associated with each of the statistical analyses conducted. Appropriate non-parametric test (e.g., Mann-Whitney U median test) was used for analysis of univariate t-test procedures where the normality assumption was violated for the continuous dependent variable.

T-tests were used to compare two groups on a continuous dependent variable (Hypotheses 1a, 5, 6, and 7b). Chi-square tests were used to examine the association between two independent variables that have two or more levels within them (Hypotheses 1b, 2, 3, 4, and 11a). The analysis of variance (ANOVA) procedure was used to compare two or more groups on a continuous dependent variable (Hypotheses 7a). The log-rank test was used to test the equality of the survival functions of two or more groups on a continuous, censored dependent variable (i.e., survival time) (Hypotheses 8a-c). The Kaplan-Meier curve was used to graph and compare the survival function of two or more groups on a continuous, censored dependent variable (i.e., survival time) (Hypotheses 8a-

c). The Cox proportional hazards regression was used to compare two groups on a continuous, censored dependent variable (i.e., survival time) while controlling for covariates (Hypotheses 9a-g and 10). The binary logistic regression analysis was used to compare two groups on a dichotomous dependent variable while controlling for covariates (Hypotheses 11b-h and 12).

All analyses were two-tailed with a significance level set at $p<0.01$. Table 3.11 below summarizes all the analyses conducted, including the corresponding study aims, hypothesis, dependent variables (DV), independent variables (IV), and measurement levels of both DV and IV.

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
AIM 1: TO COMPARE THE DEMOGRAPHIC (I.E., AGE AND GENDER), AND CLINICAL CHARACTERISTICS (I.E., HYPERLIPIDEMIA, OBESITY, HYPERTENSION, DIABETOGENIC MEDICATION USE, AND CCI SCORE) BETWEEN STATIN USERS AND NON-STATIN USERS (OBJECTIVES 1 – 6)						
Objective 1: To assess whether demographic characteristics (i.e., age and gender) differs between statin users and non-statin users						
H_{1a}: Statin users will have a significantly higher mean age compared to non-statin users	Age	Continuous	Exposure group: statin users vs. non-statin users	Dichotomous	t-test	1
H_{1b}: There is a significant association between the exposure group (i.e., statin users and non-statin users) and gender	Gender: Male vs. Female	Dichotomous	Exposure group: statin users vs. non-statin users	Dichotomous	Chi-square test	1
Objective 2: To assess whether hyperlipidemia diagnosis differs between statin users and non-statin users						
H_2: The proportion of statin users with a hyperlipidemia diagnosis will be significantly higher compared to that of non-statin users	Hyperlipidemia: Yes/No	Dichotomous	Exposure group: statin users vs. non-statin users	Dichotomous	Chi-square test	1

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
Objective 3: To assess whether obesity diagnosis differs between statin users and non-statin users						
$H_{0(3)}$: There is no significant difference in the proportion of statin users and non-statin users who have an obesity diagnosis	Obesity: Yes/No	Dichotomous	Exposure group: statin users vs. non-statin users	Dichotomous	Chi-square test	1
Objective 4: To assess whether hypertension diagnosis differs between statin users and non-statin users						
$H_{(4)}$: The proportion of statin users with a hypertension diagnosis will be significantly higher compared to that of non-statin users	Hypertension: Yes/No	Dichotomous	Exposure group: statin users vs. non-statin users	Dichotomous	Chi-square test	1

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
Objective 5: To assess whether the mean number of prescriptions for all diabetogenic medications and the mean number of prescriptions for each diabetogenic medication (i.e., thiazide diuretics, β-blockers, antipsychotics, antidepressants, immunosuppressants, and glucocorticoids) differs between statin users and non-statin users						
$H_{0(5)}$: There is no significant difference in the mean number of prescriptions for all diabetogenic medications between statin users and non-statin users	Number of prescriptions for all diabetogenic medications	Continuous	Exposure group: statin users vs. non-statin users	Dichotomous	t-test	1
$H_{0(5b\text{-}g)}$: There is no significant difference in the mean number of prescriptions for each diabetogenic medication (i.e., thiazide diuretics [**$H_{0(5b)}$**], β-blockers [**$H_{0(5c)}$**], antipsychotics [**$H_{0(5d)}$**], antidepressants[**$H_{0(5e)}$**], immunosuppressants [**$H_{0(5f)}$**], and glucocorticoids [**$H_{0(5g)}$**]) between statin users and non-statin users	Number of prescriptions for each diabetogenic medication	Continuous	Exposure group: statin users vs. non-statin users	Dichotomous	t-test	6

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
Objective 6: To compare the mean CCI score between statin users and non-statin users						
$\mathbf{H_{0(6)}}$: There is no significant difference in the mean CCI score between statin users and non-statin users	CCI score	Continuous	Exposure group: statin users vs. non-statin users	Dichotomous	t-test	1
AIM 2: TO COMPARE MEDICATION ADHERENCE AMONG USERS OF EACH STATIN TYPE, AND BETWEEN INTENSIVE-DOSE STATIN USERS AND MODERATE-DOSE STATIN USERS (OBJECTIVE 7)						
Objective 7: To assess whether medication adherence (using MPR) differs between users of each statin type, and between intensive-dose statin users and moderate-dose statin users						
$\mathbf{H_{0(7a)}}$: There is no significant difference in mean medication possession ratio (MPR) among users of each statin type	MPR	Continuous	Statin type: Atorvastatin vs. Fluvastatin vs. Lovastatin vs. Pravastatin vs. Rosuvastatin vs. Simvastatin	Nominal	ANOVA	1

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
H_{7b}: The mean medication possession ratio (MPR) will be significantly lower among intensive-dose statin users compared to moderate-dose statin users	MPR	Continuous	Statin dosage intensity: Intensive-dose vs. Moderate-dose	Dichotomous	t-test	1
AIM 3: SURVIVAL ANALYSIS – TO COMPARE TIME TO DIABETES (SURVIVAL TIME) BETWEEN STATIN USERS AND NON-STATIN USERS, BETWEEN USERS OF EACH STATIN TYPE AND NON-STATIN USERS, AND BETWEEN INTENSIVE-DOSE STATIN USERS AND MODERATE-DOSE STATIN USERS (OBJECTIVES 8 – 10)						
Objective 8: To assess whether survival times differ between statin users and non-statin users, among users of each statin type, and between intensive-dose statin users and moderate-dose statin users						
H_{8a}: Statin users will have a significantly shorter survival time compared to non-statin users	Survival time	Continuous	Exposure group: statin users vs. non-statin users	Dichotomous	Log-rank test Kaplan-Meier curves	1 1

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
$H_{0(8b)}$: There is no significant difference in the mean survival time among users of each statin type	Survival time	Continuous	Statin type: Atorvastatin vs. Fluvastatin vs. Lovastatin vs. Pravastatin vs. Rosuvastatin vs. Simvastatin	Nominal	Log-rank test Kaplan-Meier curves	1 1
H_{8c}: Intensive-dose statin users will have a shorter survival time compared to moderate-dose statin users	Survival time	Continuous	Statin dosage intensity: Intensive-dose vs. Moderate-dose	Dichotomous	Log-rank test Kaplan-Meier curves	1 1
Objective 9: To assess whether survival time differs between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for age, gender, and clinical covariates[a]						
H_{9a}: Statin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates[a]	Survival time	Continuous	Exposure group: statin users vs. non-statin users	Dichotomous	Cox proportional hazards regression	1

[a]Clinical covariates include hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score.

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
H_{9b-g}: Users of each statin type (i.e., atorvastatin [**H_{9b}**], fluvastatin [**H_{9c}**], lovastatin [**H_{9d}**], pravastatin [**H_{9e}**], rosuvastatin [**H_{9f}**], and simvastatin [**H_{9g}**]) will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates[a]	Survival time	Continuous	-Atorvastatin vs. non-statin users; -Fluvastatin vs. non-statin users; -Lovastatin vs. non-statin users; -Pravastatin vs. non-statin users; -Rosuvastatin vs. non-statin users; -Simvastatin vs. non-statin users	Nominal	Cox proportional hazards regression	6
Objective 10 : To assess whether survival times differ between intensive-dose statin users and moderate-dose statin users, while controlling for age, gender, and clinical covariates[b]						
H_{10}: Intensive-dose statin users will have a significantly shorter survival time compared to moderate-dose statin users while controlling for age, gender, and clinical covariates[b]	Survival time	Continuous	Statin dosage intensity: Intensive-dose vs. Moderate-dose	Dichotomous	Cox proportional hazards regression	1

[b]Clinical covariates include hyperlipidemia, obesity, hypertension, diabetogenic medication use, CCI score, and medication adherence.

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
AIM 4: LOGISTIC REGRESSION – TO COMPARE INCIDENCE OF DIABETES BETWEEN STATIN USERS AND NON-STATIN USERS, BETWEEN USERS OF EACH STATIN TYPE AND NON-STATIN USERS, AND BETWEEN INTENSIVE-DOSE STATIN USERS AND MODERATE-DOSE STATIN USERS (OBJECTIVES 11 & 12)						
Objective 11: To assess whether incidence of diabetes differs between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for age, gender, and clinical covariates[a]						
H_{11a}: The proportion of statin users with incident diabetes will be significantly higher than that of non-statin users	Incidence of diabetes: Yes/No	Dichotomous	Exposure group: statin users vs. non-statin users	Dichotomous	Chi-square test	1
H_{11b}: The proportion of statin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates[a]	Incidence of diabetes: Yes/No	Dichotomous	Exposure group: statin users vs. non-statin users	Dichotomous	Binary logistic regression	1

[a]Clinical covariates include hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score.

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
H_{11c-h}: The proportion of each user of statin type (i.e., atorvastatin **[H_{11c}]**, fluvastatin **[H_{11d}]**, lovastatin [**H_{11e}**], pravastatin [**H_{11f}**], rosuvastatin [**H_{11g}**], and simvastatin [**H_{11h}**]) that has incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender, and clinical covariates[a]	Incidence of diabetes: Yes/No	Dichotomous	Users of each statin type vs. non-statin users: -Atorvastatin vs. non-statin users; -Fluvastatin vs. non-statin users; -Lovastatin vs. non-statin users; -Pravastatin vs. non-statin users; -Rosuvastatin vs. non-statin users; -Simvastatin vs. non-statin users	Nominal	Binary logistic regression	6

[a]Clinical covariates include hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score.

Table 3.11: Summary of Study Aims, Objectives, Hypotheses, Study Variables, and Analyses Procedures (cont'd)						
Objectives/Hypothesis	**Dependent Variable**	**Nature of Variable**	**Independent Variable**	**Nature of Variable**	**Statistical Procedure**	**# of Tests/ Models**
Objective 12: To assess whether incidence of diabetes differs between intensive-dose statin users and moderate-dose statin users, while controlling for age, gender, and clinical covariates[b]						
H_{12}: The proportion of intensive-dose statin users with incident diabetes will be significantly higher than that of moderate-dose statin users while controlling for age, gender, and clinical covariates[b]	Incidence of diabetes: Yes/No	Dichotomous	Statin dosage intensity: Intensive-dose vs. Moderate-dose	Dichotomous	Binary logistic regression	1

[a]Clinical covariates include hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score.
[b]Clinical covariates include hyperlipidemia, obesity, hypertension, diabetogenic medication use, CCI score, and medication adherence.

CHAPTER 4: RESULTS

This chapter provides detailed descriptions of the study results, including the selection criteria and sample size requirements for the statin user and the non-statin cohorts, description of preliminary data analyses (i.e., procedures used to assess the validity of assumptions associated with each statistical analysis conducted), description of the study results structured by study objectives and corresponding hypotheses, and a summary of the study hypotheses tested.

4.1 PATIENT SELECTION CRITERIA AND SAMPLE SIZE

The study population consisted of 116,224 subjects who were aged 20 – 63 years at index date. They were followed from the earliest index date of July 1, 2003 until they had a diagnosis of diabetes or reached the end of the study period (December 31, 2004) without having diabetes diagnosis. The study population (N=116,224) was composed of an equal proportions of statin users (N=58,112) and non-statin users (N=58,112).

The sample sizes for the two cohorts met the a priori sample size requirements of N=54,843 for each group, or a total sample size of N=109,686 (given the following parameters: alpha=0.01, power=80%, effect size or relative risk of diabetes among statin users=1.25, incidence of diabetes among the unexposed=7.6 per 1,000 population, and number of the unexposed subjects to be included in the study for each exposed subject=1:1).

The statin user cohorts were: (i) subjects aged 20 – 63 years when they filled their first prescription for any statin medication including atorvastatin, fluvastatin, lovastatin,

pravastatin, rosuvastatin, and simvastatin; (ii) new statin users (i.e., did not have any statin prescription in the six months before the index date. The earliest index date was July 1, 2003. The index statin drug cases were selected within the index period of July 1, 2003 and January 1, 2004); (iii) subjects who did not fill a statin prescription that was combined with any of the non-statin lipid lowering agents; (iv) subjects who did not have a diabetes diagnosis during the six months of pre-index period; and (v) subjects who were continuously enrolled during the six months of pre-index period and for at least a year after the index date.

The non-statin user cohort were subjects who: (i) were aged 20 – 63 years when they filled their first prescription for any non-statin medication; (ii) did not receive any statin prescription; (iii) had index drug cases that were selected within a similar index period of July 1, 2003 and January 1, 2004 as statin users (for subjects with multiple drug cases, the first prescription date represented the index drug case); (iv) did not have a diagnosis of diabetes in the six months of pre-index period; and (v) were continuously enrolled during the six months of pre-index period and for at least a year after the index date.

Figures 4.1 and 4.2 describe the inclusion/exclusion criteria used in selecting both the statin user cohort and the non-statin user cohort, respectively.

Figure 4.1: Inclusion/Exclusion Criteria for the Statin Cohort

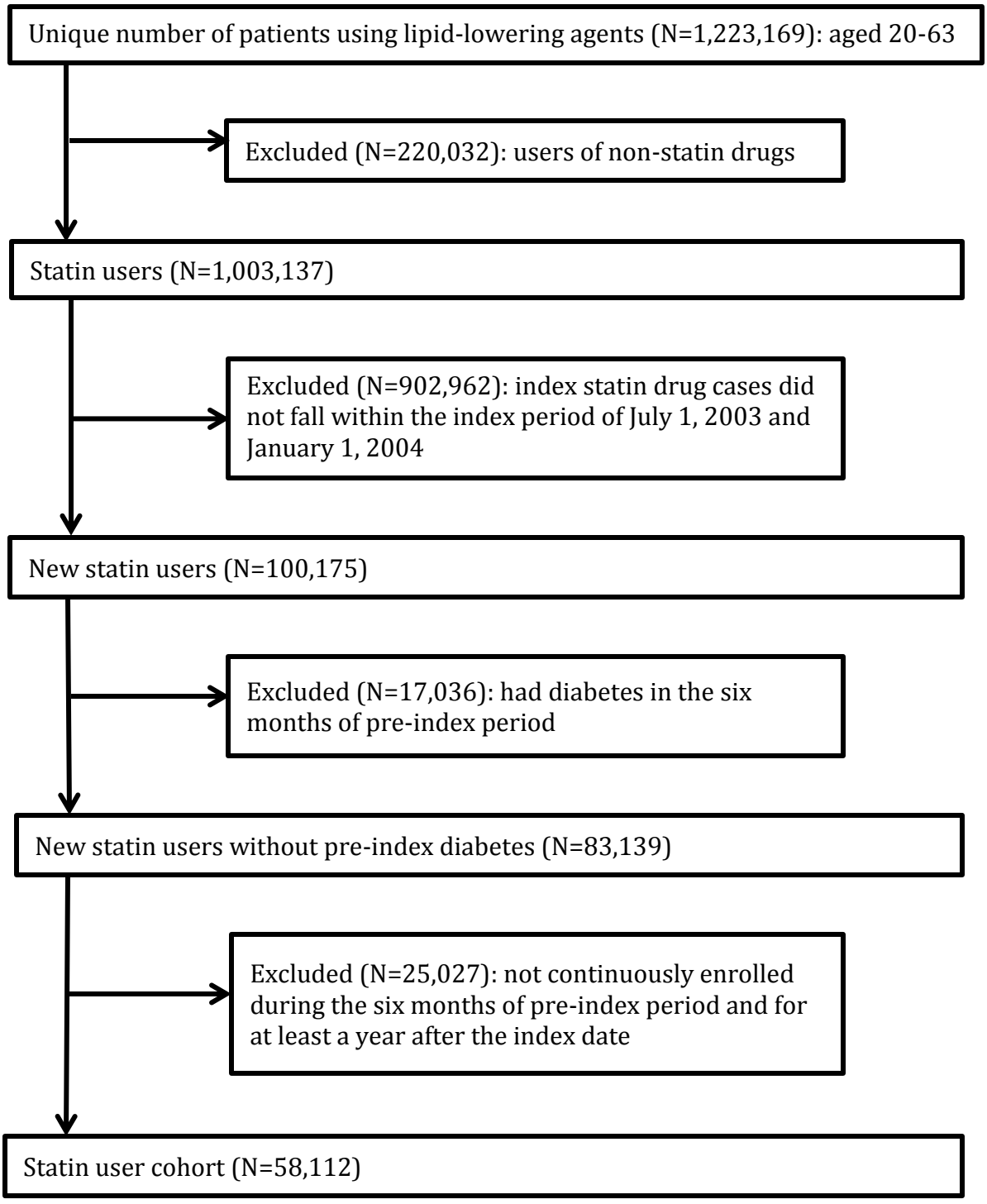
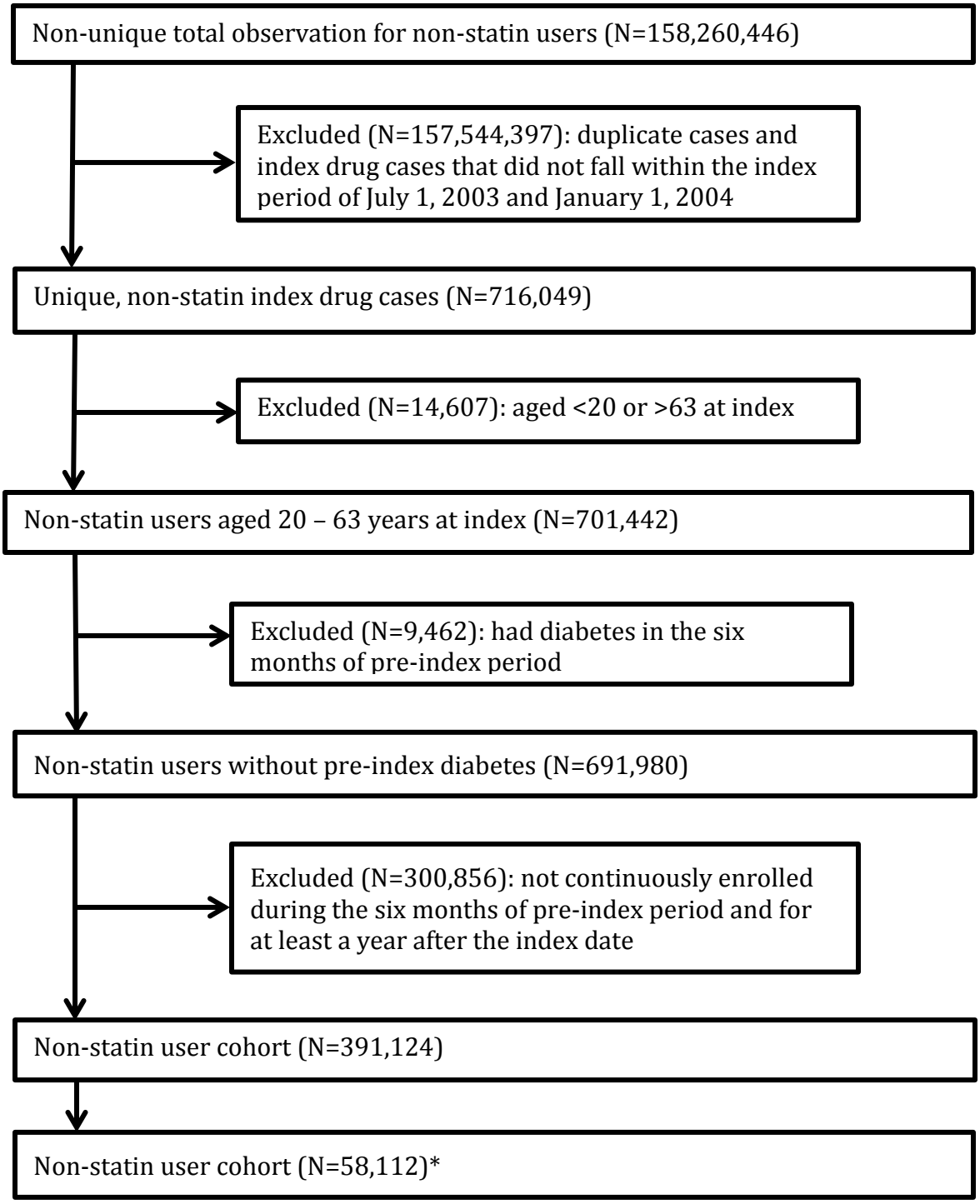


Figure 4.2: Inclusion/Exclusion Criteria for the Non-statin Cohort



*A simple random sampling (without replacement) of exactly N=58,112 from N=391,124.

4.2 PRELIMINARY DATA ANALYSIS PROCEDURES

Preliminary analysis involved examining out-of-range data values and assessing the assumptions associated with each statistical analysis conducted. Out-of-range data values were examined using the minimum and maximum functions. Out-of-range data values were set to system missing. Normality assumptions (and the Levene's test of equality of variance) were examined on continuous dependent variables such as age, number of prescriptions for all/each diabetogenic medication(s), CCI score, and MPR. The sample size assumption was examined for each chi-square analysis. Multicollinearity diagnostics (using VIF and/or Tolerance values) were examined for all predictor variables in each Cox regression and/or logistic regression model. The proportionality of hazards assumption was examined for each Cox regression model.

4.2.1 Normality

The normality assumption was examined for all continuous dependent variables (DV) such as age (hypothesis 1a), number of prescriptions for all/each diabetogenic medication(s) (hypotheses 5a-g), CCI score (hypothesis 6), and MPR (hypotheses 7a and 7b). These variables were the DVs in univariate parametric tests such as t-test and ANOVA. A formal test of normality was not used to assess the normality assumption due to sensitivity of such tests to large sample sizes.[414] However, the normality assumption

[414] Lumley T, Diehr P, Emerson S, and Chen L. The importance of the normality assumption in large public health data sets. Annu Rev Public Health. 2002;23:151-69.

was considered not violated if the absolute values of the skewness and kurtosis were not in excess of 2.[415]

In addition to the normality tests, the Levene's test of equality of variance was also assessed. In instances where the p-value associated with the Levene's test of equality of variance was less than 0.01 (i.e., significant), the value of the t-test for equality of means (and the associated degrees of freedom) corresponding to when equal variances between groups is not assumed was reported.

In all cases where the normality assumption was violated for the continuous dependent variable, the parametric t-test or ANOVA procedures were still conducted because of their robustness to violations of the normality assumption.[416] However, in such instances of normality assumption violations, appropriate non-parametric tests were also conducted (Mann-Whitney U median test and the Kruskal-Wallis test are the non-parametric equivalents of an independent samples t-test and ANOVA, respectively). The results of both the parametric and non-parametric tests were reported if a DV violates the normality assumption. Parametric tests were favored because the descriptive statistics (i.e., mean and standard deviation) were more informative than the descriptive statistics for non-parametric tests (the median value of each of the DVs that violated the normality assumption was zero for the two groups being compared).

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[415] Curran PJ, West SG, and Finch JF. The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. Psychol Methods. 1996;1(1):16-29.

[416] Lumley T et al., "The importance of the normality assumption in large public health data sets."

As mentioned earlier, the normality assumption was considered not violated if the absolute values of the skewness and kurtosis were not in excess of 2. Thus, the normality assumption was not violated for age (skewness= -0.64 and kurtosis= -0.49) and MPR (skewness= -0.89 and kurtosis= -0.29), but was violated for number of prescriptions for all/each diabetogenic medication(s) (absolute values of the skewness and kurtosis ranged from 3.16 – 64.76 and 11.48 – 5,429.19, respectively), and CCI score (skewness=8.15 and kurtosis=80.35).

See Appendix A for the full descriptive statistics and graphs associated with the evaluation of the normality assumption for all continuous dependent variables.

4.2.2 Chi-square Assumptions

Unless otherwise indicated, 0 cells (0.0%) had an expected count less than 5 for all chi-square tables reported in the results. The chi-square method assumes that a dataset is reasonably large and that tables are densely populated and well balanced (tables are unbalanced if more than 20% of the cells have an expected count less than 5). In such cases, a Fisher's exact test may be more appropriate for the analysis. Only one chi-square table was unbalanced, where 2 cells (33.3%) had an expected count of less than 5. Furthermore, all groups being compared were assumed to be independent of each other.

4.2.3 Multicollinearity

Multicollinearity occurs when two or more predictor variables (e.g., X_1, X_2, and X_3) are inter-correlated. Multicollinearity diagnostics could help assess which two or

more predictor variables are redundant with respect to one another (and thus help in deciding whether to retain or remove one or more of such variables from the model).

The multicollinearity diagnostic values were obtained by running a series of multiple regression analyses among all the predictor variables in each Cox regression model (hypotheses 9a-g and 10) and each logistic regression model (hypotheses 11b-h and 12). Because the predictor variables in each Cox regression model were also duplicated for each logistic regression model, a total of eight multiple regression multicollinearity diagnostic models were run. The number of multiple regression models corresponded to the number of main predictor variables of interest examined by the Cox and logistic regression analyses. These eight predictor variables of interest included 'Exposure' (statin users vs. non-statin users); 'Atorvastatin' (atorvastatin users vs. non-statin users); 'Fluvastatin' (fluvastatin users vs. non-statin users); 'Lovastatin' (lovastatin users vs. non-statin users); 'Pravastatin' (pravastatin users vs. non-statin users); 'Rosuvastatin' (rosuvastatin users vs. non-statin users); 'Simvastatin' (simvastatin users vs. non-statin users); and 'Intensive' (intensive-dose statin users vs. moderate-dose statin users). Other predictor variables that formed part of each multiple regression analyses included gender, hyperlipidemia, obesity, hypertension, number of prescriptions for all diabetogenic medications, CCI score, and MPR (Note: MPR was included only in the model containing the 'Intensive' variable). Because a continuous variable is required as the dependent variable in a multiple regression, age was used as the dependent variable in all multiple regression models (Note: one additional multiple regression model [Table

4.1b] evaluated the multicollinearity diagnostics for the variable 'Age' by making CCI score the dependent variable).

Evidence of multicollinearity was assumed if the Tolerance value for any variable was less than 0.1, or if the variance inflation factor (VIF) value for any of the variable was in excess of 10 [VIF = 1/Tolerance].[417]

There was no evidence of multicollinearity among the variables as shown by Tolerance values that ranged from 0.558 ('Exposure') to 0.999 ('Obesity'). Tables 4.1 – 4.8 show the full result of the Tolerance and VIF values for each variable in the multicollinearity diagnostics.

Table 4.1a: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Statin Use and Incident Diabetes

Variable	Tolerance	VIF
Exposure (statin)	0.640	1.564
Gender (male)	0.989	1.011
Hyperlipidemia	0.761	1.313
Obesity	0.998	1.002
Hypertension	0.855	1.170
Diabetogenic medications	0.849	1.177
CCI score	0.970	1.031

DV=age

[417] Kutner M, Nachtsheim C, and Neter J. In *Applied linear regression models*. New York, NY: McGraw-Hill/Irwin, 2004.

Table 4.1b: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Statin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Exposure (statin)	0.558	1.792
Age	0.736	1.358
Gender (male)	0.989	1.011
Hyperlipidemia	0.759	1.318
Obesity	0.997	1.003
Hypertension	0.850	1.177
Diabetogenic medications	0.852	1.174

DV=CCI score

Table 4.2: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Atorvastatin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Atorvastatin	0.603	1.657
Gender (male)	0.991	1.009
Hyperlipidemia	0.723	1.383
Obesity	0.998	1.002
Hypertension	0.841	1.190
Diabetogenic medications	0.838	1.194
Comorbidity index	0.969	1.032

DV=age

Table 4.3: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Fluvastatin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Fluvastatin	0.850	1.176
Gender (male)	0.991	1.009
Hyperlipidemia	0.893	1.120
Obesity	0.999	1.001
Hypertension	0.922	1.084
Diabetogenic medications	0.932	1.073
CCI score	0.990	1.010

DV=age

Table 4.4: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Lovastatin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Lovastatin	0.821	1.217
Gender (male)	0.992	1.008
Hyperlipidemia	0.929	1.076
Obesity	0.992	1.008
Hypertension	0.910	1.099
Diabetogenic medications	0.863	1.159
CCI score	0.989	1.011

DV=age

Table 4.5: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Pravastatin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Pravastatin	0.696	1.436
Gender (male)	0.991	1.009
Hyperlipidemia	0.805	1.242
Obesity	0.999	1.001
Hypertension	0.867	1.154
Diabetogenic medications	0.862	1.160
CCI score	0.975	1.025

DV=age

Table 4.6: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Rosuvastatin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Rosuvastatin	0.767	1.305
Gender (male)	0.991	1.009
Hyperlipidemia	0.832	1.202
Obesity	0.999	1.001
Hypertension	0.895	1.117
Diabetogenic medications	0.910	1.099
CCI score	0.988	1.012

DV=age

Table 4.7: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Simvastatin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Simvastatin	0.632	1.582
Gender (male)	0.994	1.006
Hyperlipidemia	0.773	1.294
Obesity	0.998	1.002
Hypertension	0.844	1.185
Diabetogenic medications	0.826	1.211
CCI score	0.960	1.042

DV=age

Table 4.8: Tolerance and VIF to test Multicollinearity among Predictor Variables in the Cox and Logistic Regression Models Evaluating the Association between Intensive-dose Statin Use and Incident Diabetes		
Variable	**Tolerance**	**VIF**
Dosage Intensity (intensive-dose)	0.990	1.010
Gender (male)	0.976	1.024
Hyperlipidemia	0.992	1.008
Obesity	0.999	1.001
Hypertension	0.974	1.027
Diabetogenic medications	0.931	1.075
CCI score	0.986	1.014
Medication possession ratio	0.971	1.029

DV=age

4.2.4 Proportionality of Hazards Assumption

An important feature of the Cox proportional hazard (Cox PH) model is that the hazard ratio (for any variable) comparing the hazard of one group to the hazard of another group is constant over time (i.e., hazard ratio is independent of time).

As mentioned in section 3.3.3.4.1 (survival analysis – the proportional hazards assumption), there are three general approaches for assessing the PH assumption. These

include a graphical procedure, a goodness-of-fit testing procedure, and a procedure that involves the use of time-dependent covariates.[418]

The third approach (a procedure that involves the use of time-dependent covariates) was employed in this dissertation because the p-value computed for each time-dependent covariate in the model – while adjusting for the effect of other variables – can be used for making more objective decision as opposed to the use of graphical methods. Time-dependent covariates were obtained by multiplying each independent variable in the model by the natural log of survival time. The PH assumption is not met for any time-dependent covariate with a p-value less than 0.01 (See Appendix B for an SPSS syntax example that can be used to run a Cox regression model with multiple time-dependent covariates).

The PH assumption was satisfied for all the major predictor variables of interest. These variables included 'Exposure' (statin users vs. non-statin users); 'Atorvastatin' (atorvastatin users vs. non-statin users); 'Fluvastatin' (fluvastatin users vs. non-statin users); 'Lovastatin' (lovastatin users vs. non-statin users); 'Pravastatin' (pravastatin users vs. non-statin users); 'Rosuvastatin' (rosuvastatin users vs. non-statin users); 'Simvastatin' (simvastatin users vs. non-statin users); and 'Intensive' (intensive-dose statin users vs. moderate-dose statin users).

However, the PH assumption was not satisfied for some variables, including some variables that were measured at baseline. Because variables such as age and gender were

[418] Kleinbaum DG and Klein M, "Evaluating the proportional hazards assumption."

defined at index (i.e., they were baseline values with single measurement at a single point in time), it was surprising that the PH assumption was not satisfied for them in some models. This means that the PH assessment considered age and gender as time-dependent variables. As a result of this observation, the PH assessment was considered not reasonable in all instances. Thus, the proportionality of hazards assumption was ignored and assumed not to be violated in all Cox regression models, and these were presented as the primary results (note again: the PH assumption was not violated for all the main predictor variables of interest).

Ignoring a violation of the PH assumption has been likened to suppressing, or not controlling for, the interaction of a variable of interest with time in regression models – a phenomenon that is known to be common among many researchers.[419] One author believed that a suppression of the PH assumption might be reasonable: (i) if the researcher does not have a strong theoretical interest in those interactions, (ii) when there is no reason to believe that the interactions with time are so strong that it would be misleading to suppress them, and (iii) due to the impracticality of testing for all possible 2-way interactions in models with moderately large number of variables.[420]

When a violation of the PH assumption is suppressed for a variable, it is acceptable to consider the coefficient estimate (and HRs) of such variables as an 'average effect' over the range of times that is observed in the data.[421]

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[419] Allison PD, "Cox models with non-proportional hazards."
[420] Ibid.
[421] Ibid.

However, sensitivity analyses of the hazards ratios (while controlling for variables that did not satisfy the PH assumption) were conducted. The hazard ratios (and 99% confidence interval of the hazard ratios) for the sensitivity analyses were presented alongside those of the primary results. The magnitude of the hazard ratios increased when time-dependent covariates were controlled for in all Cox regression models (the specifics of each variable that failed to satisfy the PH assumption test is discussed in section 4.5 of the results).

Appendix C shows the full model results of the sensitivity analyses when time-dependent covariates were controlled for in all Cox regression models.

4.3 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The current study had four study aims. The first aim of the study was to compare the descriptive statistics (mean, median, minimum, maximum, frequency, and percent) of demographic (i.e., age and gender) and clinical (i.e., hyperlipidemia, obesity, hypertension, number of prescriptions for all/each diabetogenic medication(s), and CCI score) variables between statin users and non-statin users (objectives 1 – 6). The main purpose of objectives 1 – 6 was to examine if statin users and non-statin users differed significantly on any of these demographic and clinical variables. A significant difference or association on any of the variable(s) warranted controlling for such variable(s) in the regression models (Cox regression and logistic regression) that was used to examine the differential risk of incident diabetes between statin users and non-statin users.

Furthermore, the second aim of the study was to compare MPR among users of each statin type and between intensive-dose statin users and moderate-dose statin users (objective 7). The third (objectives 8 – 10) and fourth (objectives 11 and 12) study aims primarily compared survival time and incidence of diabetes between statin users and non-statin users using Cox regression and logistic regression models, respectively. These study aims are further discussed in sections 4.4 – 4.6.

The first and second study aims are mainly descriptive in nature and are presented in this section. The study results are organized by study objectives and corresponding hypotheses.

4.3.1 Demographic Variables

Objective 1 examined whether statin users and non-statin users differed significantly on demographic characteristics. Age and gender were the only demographic information available in the *MarketScan* data used for this project. Race/ethnicity information is an important demographic variable that would have been ideal to control for but was not available in the data.

Objective 1: To assess whether demographic characteristics (i.e., age and gender) differed between statin users and non-statin users.

4.3.1.1 Age

Age is a continuous variable that was defined as the age (in years) when subjects received their first index medication. Mean age was compared between statin users and non-statin users. In addition, the association between exposure status (i.e., statin users vs. non-statin users) and age was examined by categorizing age into four groups (i.e., 20 – 34, 35 – 44, 45 – 54, and 55 – 63).

H_{1a}: Statin users will have a significantly higher mean age compared to non-statin users.

Table 4.9 shows the descriptive statistics of age between statin users and non-statin users. The age at index ranged from 20 to 63 years for statin users, while age at index ranged from 20 to 62 years for non-statin users. The table shows that the mean age (SD) for the study population (N=116,224) was 46.4 (11.6) while the median age was 49 years. An independent samples t-test showed that mean age was significantly higher

among statin users (52.2, SD=7.8) compared to non-statin users (40.6, SD=11.9) (t=197.2; df=100,418.5; p<0.0001). [**Conclusion: alternative hypothesis H_{1a} was supported].**

Table 4.9: Descriptive Statistics of Age for Statin Users and Non-statin Users

Age[a]	**Statin Users**	**Non-statin Users**	**Study Population**
Mean (SD)	52.2 (7.8)	40.6 (11.9)	46.4 (11.6)
Median	54	41	49
Minimum	20	20	20
Maximum	63	62	63
Number of cases	58,112	58,112	116,224
			t-test (t=197.2; df=100,418.5; p<0.0001)

[a]Weighted mean (SD) age for statin users, non-statin users, and the study population are 53.3 (7.1), 42.0 (11.9), and 48.1 (11.1), respectively.
MarketScan weights*: MarketScan* person-level national weights (included as a weight variable in the data) were constructed utilizing weight estimates from the Household Component of the Medical Expenditure Panel Survey (MEPS). MEPS's weights accounts for demographic variables that includes region (Northeast, North Central, South, West); age (0 – 17, 18 – 44, 45 – 64); and sex (male, female). The *MarketScan* weight is the ratio of MEPS-based estimates in the different age/sex/region categories and the *MarketScan* number in the same category.

Age Categories

Table 4.10 shows the age group distribution for statin users and non-statin users. A chi-square test showed that there was a significant association of exposure status (i.e., statin users vs. non-statin users) and age categories (χ^2 = 27,715.5; df=3; p<0.0001). The majority of statin users (83.6%, N=48,573) were aged 45 years and above while the majority of non-statin users (59.6%, N=34,613) were aged below 45 years.

Table 4.10: Frequency and Percent of Statin Users and Non-statin Users by Age Group

Age Group	Statin Users N (%)	Non-statin Users N (%)	Study Population N (%)
20 – 34	1,728 (3.0)	18,747 (32.3)	20,475 (17.6)
35 – 44	7,811 (13.4)	15,866 (27.3)	23,677 (20.4)
45 – 54	21,909 (37.7)	15,167 (26.1)	37,076 (31.9)
55 – 63	26,664 (45.9)	8,332 (14.3)	34,996 (30.1)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)

χ^2 = 27,715.5; df=3; p<0.0001

Age and Dosage Intensity

A sub-analysis among the statin user group (N=58,112) showed that mean age was not significantly different between intensive-dose statin users (52.0, SD=7.9) and moderate-dose statin users (52.3, SD=7.8) (t=2.5; df=58,110; p=0.011). When stratified by age categories, a chi-square test shows that there was no significant association of statin dosage intensity (i.e., intensive-dose statin users vs. moderate-dose statin users) and age categories (χ^2 = 2.70; df=3; p=0.44). The proportion of intensive-dose statin users (83.1%, N=5,153) and moderate-dose statin users (83.7%, N=43,420) who were 45 years and above was similar.

Table 4.11 shows the descriptive statistics of age for intensive-dose and moderate-dose statin users, while Table 4.12 shows the age group distribution for intensive-dose and moderate-dose statin users.

Table 4.11: Descriptive Statistics of Age for Intensive-dose and Moderate-dose Statin Users

Age	Intensive-dose	Moderate-dose	Statin Users
Mean (SD)	52.0 (7.9)	52.3 (7.8)	52.2 (7.8)
Median	53	54	54
Minimum	20	20	20
Maximum	63	63	63
Number of cases	6,205	51,907	58,112
			t-test (t=2.5; df=58,110; p=0.011)

Table 4.12: Frequency and Percent of Intensive-dose and Moderate-dose Statin Users by Age Group

Age Group	Intensive-dose N (%)	Moderate-dose N (%)	Statin Users N (%)
20 – 34	198 (3.2)	1,530 (2.9)	1,728 (3.0)
35 – 44	854 (13.8)	6,957 (13.4)	7,811 (13.4)
45 – 54	2,355 (38.0)	19,554 (37.7)	21,909 (37.7)
55 – 63	2,798 (45.1)	23,866 (46.0)	26,664 (45.9)
Total	6,205 (100.0)	51,907 (100.0)	58,112 (100.0)

$\chi^2 = 2.7$; df=3; p=0.44

4.3.1.2 Gender

Gender is a dichotomous variable (1=male, 0=female) that was defined as the sex of each subject when they received the index medication.

H_{1b}: There is a significant association between the exposure group (i.e., statin users and non-statin users) and gender.

Table 4.13 shows gender distribution for statin users and non-statin users. The majority (51.1%, N=59,421) of the study population were males. A chi-square analysis showed that there was a significant association of exposure group (i.e., statin users vs. non-statin users) and gender ($\chi^2 = 41.7$; df=1; $p<0.0001$). The proportion of statin users that are males (50.2%, N=29,160) was higher compared to the proportion of statin users that are females (49.8%, N=28,952). Similarly, the proportion of non-statin users that are males (52.1%, N=30,261) was higher compared to the proportion of non-statin users that are females (47.9%, N=27,851). [**Conclusion: hypothesis H_{1b} was supported].**

Table 4.13: Frequency and Percent of Statin Users and Non-statin Users by Gender

Gender[a]	Statin Users N (%)	Non-statin Users N (%)	Study Population N (%)
Male	29,160 (50.2)	30,261 (52.1)	59,421 (51.1)
Female	28,952 (49.8)	27,851 (47.9)	56,803 (48.9)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)

$\chi^2 = 41.7$; df=1; $p<0.0001$

[a]Weighted values: the proportion of statin users and non-statin users that are males are 30.3% (N=812,956) and 29.9% (N=685,917), respectively. The proportion of the study population that are males and females are 30.1% (N=1,498,873) and 69.9% (N=3,480,394), respectively.

4.3.2 Clinical Variables

Objectives 2 – 6 examined whether statin users and non-statin users differed on certain clinical characteristics that are considered important risk factors for diabetes mellitus. These clinical characteristics include the presence or absence of hyperlipidemia (objective 2), obesity (objective 3), and hypertension (objective 4), number of prescriptions for all/each diabetogenic medication(s) (objective 5), and the CCI score (objective 6). Other clinical variables that would have been important to control for but were not available in the *MarketScan* data include family history of diabetes, physical activity level, cholesterol level (HDL-C, LDL-C, TG), height and weight data (thus BMI), and presence or absence of prediabetes.

4.3.2.1 Hyperlipidemia

Hyperlipidemia (or hyperlipidemia diagnosis) is a dichotomous variable that was defined as the presence or absence of at least one hyperlipidemia diagnosis at or before the index date. The hyperlipidemia diagnosis variable was identified using ICD-9-CM codes 272.0 (pure hypercholesterolemia: high TC), 272.1 (pure hypertriglyceridemia: high TG), 272.2 (mixed hyperlipidemia: high LDL-C, high TG, and low HDL-C), and 272.4 (other and unspecified hyperlipidemia).

Objective 2: To assess whether hyperlipidemia diagnosis differed between statin users and non-statin users.

H_2: The proportion of statin users with a hyperlipidemia diagnosis will be significantly higher compared to that of non-statin users.

Table 4.14 shows hyperlipidemia diagnosis distribution for statin users and non-statin users. For the total study population, 28.0% (N=35,516) had a diagnosis of hyperlipidemia. A chi-square analysis showed that there was a significant difference in the proportion of statin users and non-statin users with a hyperlipidemia diagnosis (χ^2 = 27,526.9; df=1; p<0.0001). The proportion of statin users with a hyperlipidemia diagnosis (49.8%, N=28,953) was higher compared to the proportion of non-statin users with a hyperlipidemia diagnosis (6.1%, N=3,563). [**Conclusion: hypothesis H_2 was supported].**

Table 4.14: Frequency and Percent of Statin Users and Non-statin Users by Hyperlipidemia Diagnosis

Hyperlipidemia	Statin Users N (%)	Non-statin Users N (%)	Study Population N (%)
Yes	28,953 (49.8)	3,563 (6.1)	32,516 (28.0)
No	29,159 (50.2)	54,549 (93.9)	83,708 (72.0)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)

χ^2 = 27,526.9; df=1; p<0.0001

4.3.2.2 Obesity

Obesity (or obesity diagnosis) is a dichotomous variable that was defined as the presence or absence of at least one obesity diagnosis at or before the index date. The obesity diagnosis variable was identified using ICD-9-CM codes 278.00 (obesity, unspecified) and 278.01 (morbid obesity).

Objective 3: To assess whether obesity diagnosis differed between statin users and non-statin users**.**

$H_{0(3)}$: There is no significant difference in the proportion of statin users and non-statin users who have an obesity diagnosis.

Table 4.15 shows obesity diagnosis distribution for statin users and non-statin users. For the total study population, 0.6% (N=753) had a diagnosis of obesity. A chi-square analysis showed that there was a significant difference in the proportion of statin users and non-statin users with an obesity diagnosis (χ^2 = 206.4; df=1; p<0.0001). The proportion of statin users with an obesity diagnosis (1.0%, N=573) was higher compared to the proportion of non-statin users with an obesity diagnosis (0.3%, N=180).

[Conclusion: Null hypothesis $H_{0(3)}$ was rejected].

Table 4.15: Frequency and Percent of Statin Users and Non-statin Users by Obesity Diagnosis

Obesity	Statin Users N (%)	Non-statin Users N (%)	Study Population N (%)
Yes	573 (1.0)	180 (0.3)	753 (0.6)
No	57,539 (99.0)	57,932 (99.7)	115,471 (99.4)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)

χ^2 = 206.4; df=1; p<0.0001

4.3.2.3 Hypertension

Hypertension (or hypertension diagnosis) is a dichotomous variable that was defined as the presence or absence of at least one hypertension diagnosis at or before the index date. The hypertension diagnosis variable was identified using ICD-9-CM codes 401.0 (malignant essential hypertension), 401.1 (benign essential hypertension), and 401.9 (unspecified essential hypertension).

Objective 4: To assess whether hypertension diagnosis differed between statin users and non-statin users**.**

H_4: The proportion of statin users with a hypertension diagnosis will be significantly higher compared to that of non-statin users.

Table 4.16 shows hypertension diagnosis distribution for statin users and non-statin users. For the total study population, 17.5% (N=20,348) had a diagnosis of hypertension. A chi-square analysis showed that there was a significant difference in the proportion of statin users and non-statin users with a hypertension diagnosis (χ^2 = 14,257.5; df=1; p<0.0001). The proportion of statin users with a hypertension diagnosis (30.8%, N=17,909) was higher compared to the proportion of non-statin users with a hypertension diagnosis (4.2%, N=2,439). [**Conclusion: alternative hypothesis H_4 was supported].**

Table 4.16: Frequency and Percent of Statin Users and Non-statin Users by Hypertension Diagnosis			
Hypertension	**Statin Users N (%)**	**Non-statin Users N (%)**	**Study Population N (%)**
Yes	17,909 (30.8)	2,439 (4.2)	20,348 (17.5)
No	40,203 (69.2)	55,673 (95.8)	95,876 (82.5)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
$\chi^2 = 14{,}257.5$; df=1; p<0.0001			

4.3.2.4 Diabetogenic Medication Use

Objective 5 examined whether statin users and non-statin users differed in the mean number of prescriptions for all/each diabetogenic medication(s) they received. If one group was exposed to a higher amount of diabetogenic drugs, then that group may be more predisposed to have an increased risk of diabetes that is independent of the effects of statin use. Thus, the number of prescriptions for all/each diabetogenic medication(s) received by statin users and non-statin users was compared and accounted for in all regression analyses.

The 'number of prescriptions for all diabetogenic medications' is a continuous variable that was obtained by summing the number of days supplied for all diabetogenic medications during the observation period (the observation period was defined as the time between the start of the pre-index period and the date of diabetes diagnosis or the end of the study period if there was no occurrence of diabetes). These diabetogenic medication variables (identified using the therapeutic class 'THERCLS' variable) included thiazide diuretics, beta-blockers, antipsychotics, antidepressants,

immunosuppressants, and glucocorticoids. One prescription fill was defined as a 30-day supply of the diabetogenic medication.

Furthermore, the 'number of prescriptions for each diabetogenic medication' is a continuous variable that was obtained by summing the number of days supplied for each diabetogenic medication during the observation period. One prescription fill was also defined as a 30-day supply of the diabetogenic medication.

Objective 5: To assess whether the mean number of prescriptions for all diabetogenic medications and the mean number of prescriptions for each diabetogenic medication differed between statin users and non-statin users.

4.3.2.4.1 Number of prescriptions for all diabetogenic medications

$H_{0(5a)}$: There is no significant difference in the mean number of prescriptions for all diabetogenic medications between statin users and non-statin users.

Table 4.17 shows the descriptive statistics of 'number of prescriptions for all diabetogenic medications' for statin users and non-statin users.

The mean (SD) number of prescriptions for all diabetogenic medications for the study population (N=116,224) was 3.2 (7.1). An independent samples t-test showed that the mean number of prescriptions received for all diabetogenic medications by statin users (5.7, SD=9.0) was significantly higher than that received by non-statin users (0.8, SD=3.0) (t=123.3; df=71,250.0; $p<0.0001$).

Because the 'number of prescriptions for all diabetogenic medications' variable was not normally distributed, an independent samples Mann-Whitney U median test also

showed that the median (and the distribution of the median) number of prescriptions for all diabetogenic medications was not the same across levels of the exposure group ($p<0.0001$). Thus, there was a significant difference in the mean (or median) number of prescriptions for all diabetogenic medications received by statin users and non-statin users. [**Conclusion: null hypothesis $H_{0(5a)}$ was rejected].**

Table 4.17: Descriptive Statistics of Number of Prescriptions for All Diabetogenic Medications for Statin Users and Non-statin Users

Number of prescriptions for all diabetogenic medications[a]	Statin Users	Non-statin Users	Study Population
Mean (SD)	5.66 (8.97)	0.82 (3.04)	3.24 (7.12)
Median	0	0	0
Minimum	0	0	0
Maximum	107	71	107
Number of cases	58,112	58,112	116,224
			t-test (t=123.3; df=71,250; p<0.0001)

[a]One prescription is equivalent to a 30-day supply of all diabetogenic medications filled over the observation period.

Categorized 'number of prescriptions for all diabetogenic medications'

Table 4.18 shows the distribution for the categorized 'number of prescriptions for all diabetogenic medications' for statin users and non-statin users. A chi-square test showed that there was a significant association of exposure status (i.e., statin users vs. non-statin users) and the 'number of prescriptions for all diabetogenic medications' categories (χ^2 = 17,069.4; df=3; $p<0.0001$). The majority of statin users (55.3%, N=32,112) and non-statin users (87.7%, N=50,979) did not receive any diabetogenic

medication prescription. However, the proportion of statin users with at least one diabetogenic medication prescription (44.7%, N=26,000) was higher compared to the proportion of non-statin users with at least one diabetogenic medication prescription (12.3%, N=7,133).

Table 4.18: Frequency and Percent of Statin Users and Non-statin Users by Number of Prescriptions for All Diabetogenic Medications

Number of prescriptions for all diabetogenic medications[a]	Statin Users N (%)	Non-statin Users N (%)	Study Population N (%)
0	32,112 (55.3)	50,979 (87.7)	83,091 (71.5)
1 – 5	6,224 (10.7)	3,945 (6.8)	10,169 (8.7)
6 – 10	5,832 (10.0)	1,645 (2.8)	7,477 (6.4)
>10	13,944 (24.0)	1,543 (2.7)	15,487 (13.3)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)

$\chi^2 = 17{,}069.4$; df=3; $p<0.0001$

[a]One prescription is equivalent to a 30-day supply of all diabetogenic medications filled over the observation period.

4.3.2.4.2 Number of prescriptions for each diabetogenic medication

$H_{0(5b\text{-}g)}$: There is no significant difference in the mean number of prescriptions for each diabetogenic medication (i.e., thiazide diuretics [**$H_{0(5b)}$**], β-blockers [**$H_{0(5c)}$**], antipsychotics [**$H_{0(5d)}$**], antidepressants[**$H_{0(5e)}$**], immunosuppressants [**$H_{0(5f)}$**], and glucocorticoids [**$H_{0(5g)}$**]) between statin users and non-statin users**.**

Table 4.19 shows the descriptive statistics of 'number of prescriptions for each diabetogenic medication' for statin users and non-statin users. Independent samples t-tests in Table 4.19 shows that the mean number of prescriptions for each diabetogenic medication (except those of glucocorticoids) was significantly higher among statin users compared to non-statin users.

Because the distributions of 'number of prescriptions for each diabetogenic medication' variables were not normal, independent samples Mann-Whitney U median tests also showed that the median (and the distributions of the median) number of prescriptions for thiazides, beta-blockers, antipsychotics, antidepressants, and immunosuppressants were significantly ($p<0.0001$) different across levels of the exposure group (i.e., statin users and non-statin users). However, the median (and the distribution of the median) number of prescriptions for glucocorticoids was not significantly different ($p=0.098$) between statin users and non-statin users.

Thus, there was a significant difference in the mean (or median) number of prescriptions for each diabetogenic medication received by statin users and non-statin

users (except those of glucocorticoids). [**Conclusion: null hypotheses $H_{0(5b-f)}$ were rejected, but null hypothesis $H_{0(5g)}$ was not rejected].**

Table 4.19: Descriptive Statistics of Number of Prescriptions for Each Diabetogenic Medication for Statin Users and Non-statin Users

Number of prescriptions for each diabetogenic medication[a]	Statin Users	Non-statin Users
Thiazide diuretics		
Mean (SD)	0.73 (2.85)	0.11 (0.97)
Median	0	0
Minimum	0	0
Maximum	37	20
Number of cases	58,112	58,112
		t-test (t=49.7; df=71,268.6; p<0.0001)
Beta-blockers		
Mean (SD)	2.23 (4.94)	0.02 (1.46)
Median	0	0
Minimum	0	0
Maximum	38	25
Number of cases	58,112	58,112
		t-test (t=94.3; df=68,237.6; p<0.0001)
Antipsychotics		
Mean (SD)	0.12 (1.32)	0.02 (0.45)
Median	0	0
Minimum	0	0
Maximum	50	27
Number of cases	58,112	58,112
		t-test (t=17.5; df=71,251; p<0.0001)

Table 4.19: Descriptive Statistics of Number of Prescriptions for Each Diabetogenic Medication for Statin Users and Non-statin Users (cont'd)		
Number of prescriptions for each diabetogenic medication	**Statin Users**	**Non-statin Users**
Antidepressants		
Mean (SD)	2.52 (5.82)	0.47 (2.13)
Median	0	0
Minimum	0	0
Maximum	94	69
Number of cases	58,112	58,112
		t-test (t=79.9; df=73,426.3; p<0.0001)
Immunosuppressants		
Mean (SD)	0.05 (1.11)	0.005 (0.241)
Median	0	0
Minimum	0	0
Maximum	64	29
Number of cases	58,112	58,112
		t-test (t=10.3; df=63,611.2; p<0.0001)
Glucocorticoids		
Mean (SD)	0.004 (0.102)	0.002 (0.077)
Median	0	0
Minimum	0	0
Maximum	9.93	9.50
Number of cases	58,112	58,112
		t-test (t=2.4; df=108,817; p=0.016)

[a]One prescription is equivalent to a 30-day supply of each diabetogenic medication filled over the observation period.

Categorized 'number of prescriptions for each diabetogenic medication'

Table 4.20 shows the distribution of the categorized 'number of prescriptions for each diabetogenic medication' for statin users and non-statin users. A chi-square test showed that there was a significant association of exposure status (i.e., statin users vs. non-statin users) and the 'number of prescriptions for each diabetogenic medication' categories for each diabetogenic medication except glucocorticoids.

The majority of statin users and non-statin users, respectively, did not receive any prescription for thiazide diuretics (91.3% vs. 98.1%), beta-blockers (78.2% vs. 96.8%), antipsychotics (98.6% vs. 99.7%), antidepressants (75.5% vs. 91.7%), immunosuppressants (99.6% vs. 99.9%), and glucocorticoids (99.90% vs. 99.94%). However, the proportion of statin users who received at least one diabetogenic medication prescription was higher compared to the proportion of non-statin users who received at least one diabetogenic medication prescription, respectively, for thiazide diuretics (8.7% vs. 1.9%), beta-blockers (21.8% vs. 3.1%), antipsychotics (1.4% vs. 0.4%), antidepressants (24.6% vs. 8.3%), and immunosuppressants (0.40% vs. 0.06%). However, the proportion of statin users (0.10%, N=56) and non-statin users (0.06%, N=33) who received at least one glucocorticoid prescription was similar.

Table 4.20: Frequency and Percent of Statin Users and Non-statin Users by Number of Prescriptions for Each Diabetogenic Medication			
Number of prescriptions for each diabetogenic medication[a]	**Statin Users N (%)**	**Non-statin Users N (%)**	**Total N (%)**
Thiazide diuretics			
0	53,073 (91.3)	57,034 (98.1)	110,107 (94.7)
1 – 5	1,828 (3.1)	624 (1.1)	2,452 (2.1)
6 – 10	1,424 (2.5)	280 (0.5)	1,704 (1.5)
>10	1,787 (3.1)	174 (0.3)	1,961 (1.7)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 2,828.5; df=3; p<0.0001			
Beta-blockers			
0	45,459 (78.2)	56,263 (96.8)	101,722 (87.5)
1 – 5	2,886 (5.0)	872 (1.5)	3,758 (3.2)
6 – 10	3,443 (5.9)	484 (0.8)	3,927 (3.4)
>10	6,324 (10.9)	493 (0.8)	6,817 (5.9)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 9,444.1; df=3; p<0.0001			
Antipsychotics			
0	57,324 (98.6)	57,909 (99.7)	115,233 (99.1)
1 – 5	328 (0.6)	127 (0.2)	455 (0.4)
6 – 10	171 (0.3)	44 (0.1)	215 (0.2)
>10	289 (0.5)	32 (0.1)	321 (0.3)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 372.5; df=3; p<0.0001			

Table 4.20: Frequency and Percent of Statin Users and Non-statin Users by Number of Prescriptions for Each Diabetogenic Medication (cont'd)			
Number of prescriptions for each diabetogenic medication[a]	**Statin Users N (%)**	**Non-statin Users N (%)**	**Total N (%)**
<u>Antidepressants</u>			
0	43,846 (75.5)	53,290 (91.7)	97,136 (83.6)
1 – 5	4,581 (7.9)	2,996 (5.2)	7,577 (6.5)
6 – 10	3,480 (6.0)	1,064 (1.8)	4,544 (3.9)
>10	6,205 (10.7)	762 (1.3)	6,967 (6.0)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 6,786.7; df=3; p<0.0001			
<u>Immunosuppressants</u>			
0	57,887 (99.60)	58,077 (99.94)	115,964 (99.78)
1 – 5	61 (0.10)	17 (0.03)	78 (0.10)
6 – 10	46 (0.10)	7 (0.01)	53 (0.05)
>10	118 (0.20)	11 (0.02)	129 (0.10)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 142.6; df=3; p<0.0001			
<u>Glucocorticoids</u>			
0	58,056 (99.90)	58,079 (99.94)	116,135 (99.92)
1 – 5	53 (0.09)	30 (0.05)	83 (0.07)
6 – 10	3 (0.01)	3 (0.01)	6 (0.01)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 6.4[b]; df=2; **p=0.04**			

[a]One prescription is equivalent to a 30-day supply of each diabetogenic medication filled over the observation period.
[b]2 cells (33.3%) had an expected count less than 5. The minimum expected count was 3.

4.3.2.5 Charlson Comorbidity Index Score

The CCI score is a continuous weighted (higher weight is assigned to more severe conditions) variable that was calculated by summing the weights (i.e., 1, 2, 3, or 6) assigned to a set of diagnostic conditions and/or procedures (identified using the ICD-9-CM diagnostic and procedure codes) that were present at or prior to the start of the index medication use. For example, a patient with comorbid conditions of congestive heart failure (1), ulcer (1), leukemia (2), and liver disease (3) will have a CCI score of 7. The higher the CCI score for a patient, the higher the risk of mortality associated with such two or more comorbid conditions in the patient. Because diabetes is often comorbid with other diseases such as coronary heart disease, individuals with higher CCI scores might have increased risk of diabetes. Therefore, the CCI score was controlled for in all regression models examining the risk of diabetes between statin users and non-statin users.

Objective 6: To compare the mean CCI score between statin users and non-statin users.

$H_{0(6)}$: There is no significant difference in the mean CCI score between statin users and non-statin users.

Table 4.21 shows the descriptive statistics of CCI scores for statin users and non-statin users. The mean (SD) CCI score for the study population (N=116,224) was 0.15 (0.73). An independent samples t-test showed that the mean CCI score was significantly higher among statin users (0.25, SD=0.94) compared to non-statin users (0.04, SD=0.39) (t=48.6; df=78,093.9; p<0.0001).

Because the CCI score variable was not normally distributed, an independent samples Mann-Whitney U median test also showed that the median CCI score (and the distribution of the median CCI score) was not the same across levels of the exposure group ($p<0.0001$). Thus, there was a significant difference in the mean (or median) CCI score between statin users and non-statin users. [**Conclusion: null hypothesis $H_{0(6)}$ was rejected].**

Table 4.21: Descriptive Statistics of Charlson Comorbidity Index Score for Statin Users and Non-statin Users

Charlson Comorbidity Index Score	Statin Users	Non-statin Users	Study Population
Mean (SD)	0.25 (0.94)	0.04 (0.39)	0.15 (0.73)
Median	0	0	0
Minimum	0	0	0
Maximum	15	11	15
Number of cases	58,112	58,112	116,224
			t-test (t=48.6; df=78,093.9; p<0.0001)

Categorized 'Charlson Comorbidity Index Score'

Table 4.22 shows the distribution of the categorized CCI score for statin users and non-statin users. A chi-square test showed that there was a significant association of exposure status (i.e., statin users vs. non-statin users) and the CCI score categories (χ^2 = 4,667; df=3; $p<0.0001$). The majority of statin users (87.1%, N=50,631) and non-statin users (97.7%, N=56,792) had zero CCI scores. However, the proportion of statin users with CCI scores of one or more (12.9%, N=7,481) was higher compared to the proportion of non-statin users with CCI scores of one or more (2.3%, N=1,320).

Table 4.22: Frequency and Percent of Statin Users and Non-statin Users by Charlson Comorbidity Index Score Categories			
CCI score categories	**Statin Users N (%)**	**Non-statin Users N (%)**	**Study Population N (%)**
0	50,631 (87.1)	56,792 (97.7)	107,423 (92.4)
1 – 5	6,794 (11.7)	1,212 (2.1)	8,006 (6.9)
6 – 10	678 (1.2)	107 (0.2)	785 (0.7)
>10	9 (0.015)	1 (0.002)	10 (0.009)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
$\chi^2 = 4{,}667$; df=3; p<0.0001			

4.3.3 Medication Possession Ratio (Medication Adherence)

The second aim of the study was to compare medication adherence (using the medication possession ratio) among users of each statin type (objective 7, hypothesis 7a) and between intensive-dose statin users and moderate-dose statin users (objective 7, hypothesis 7b). MPR is a continuous variable (for the purpose of all regression analyses) that was defined as the sum of number of days of statin prescription supplied (minus the number of days supplied for the last statin prescription) divided by the sum of days between the first and last statin prescription fill dates.

For descriptive purposes, statin users were also categorized into those who were adherent (MPR ≥80%) or not adherent (MPR<80%) with their statin medications (Note: MPR values greater than 100% were truncated to 100%). MPR is a measure of medication adherence, with higher MPR values indicating higher adherence or compliance with the statin medication. MPR was compared among users of six statin types (i.e., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin), as well as between intensive-dose statin users and moderate dose statin users.

Objective 7: To assess whether medication adherence (using MPR) differed among users of each statin type, and between intensive-dose statin users and moderate-dose statin users.

4.3.3.1 Statin Types and Medication Adherence

$H_{0(7a)}$: There is no significant difference in mean MPR among users of each statin type.

Table 4.23 shows the descriptive statistics of MPR (in percent) by statin type and the frequency and percent of use of each statin type. The table shows that the most frequently prescribed statins were atorvastatin (50.7%, N=29,474) and simvastatin (23.1%, N=13,415), while the least prescribed statin was fluvastatin (3.1%, N=1,799).

The mean (SD) MPR among all statin users (N=50,557) was 75.0 (25.3). A one-way ANOVA showed that there was at least one significant difference in mean MPR among users of each statin type ($F=29.1$; $df=5$; $p<0.0001$). Mean MPR was highest among lovastatin users (79.6, SD=24.2) but decreased, consecutively, among rosuvastatin (76.5, SD=23.9), atorvastatin (74.8, SD=25.3), pravastatin (74.5, SD=25.5), and simvastatin (74.3, SD=25.6) users. Fluvastatin users (72.8, SD=26.4) had the lowest mean MPR. Thus, there was at least one significant difference in mean MPR among users of each statin type. [**Conclusion: null hypothesis $H_{0(7a)}$ was rejected].**

Post-hoc Analysis

There are 15 possible two-way multiple comparisons in a group with six different statin types (i.e., number of comparison $=N(N-1)/2$, where N equals the number of levels in the group). A post-hoc multiple comparison analysis indicated that mean MPR was significantly higher for lovastatin users (79.6) compared to rosuvastatin (76.5, $p<0.0001$), atorvastatin (74.8, $p<0.0001$), pravastatin (74.5, $p<0.0001$), simvastatin (74.3, $p<0.0001$), and fluvastatin (72.8, $p<0.0001$) users. In addition, mean MPR was significantly higher for rosuvastatin users (76.5) compared to simvastatin (74.3, $p=0.001$) and fluvastatin (72.8, $p<0.0001$) users. All the other eight possible two-way multiple

comparisons of the mean MPRs were not statistically different (i.e., $p \geq 0.01$) from each other.

Table 4.23: Descriptive Statistics of Medication Possession Ratio by Types of Statin						
Type of Statin	**Mean (SD)**	**Median**	**Minimum**	**Maximum**	**N (%)[a]**	**N (%)[b]**
Lovastatin	79.6 (24.2)	90.4	0.2	100	3,329 (6.6)	4,054 (7.0)
Rosuvastatin	76.5 (23.9)	84.1	4	100	2,608 (5.2)	2,987 (5.1)
Atorvastatin	74.8 (25.3)	82.9	3	100	25,948 (51.3)	29,474 (50.7)
Pravastatin	74.5 (25.5)	82.6	3	100	5,472 (10.8)	6,383 (11.0)
Simvastatin	74.3 (25.6)	82.3	0.4	100	11,677 (23.1)	13,415 (23.1)
Fluvastatin	72.8 (26.4)	81.1	3	100	1,523 (3.0)	1,799 (3.1)
Statin users	75.0 (25.3)	83.3	0.2	100	50,557 (100.0)	58,112 (100.0)
						ANOVA (F=29.1; df=5; p<0.0001)

[a]Total N was less than 58,112 because of missing values for MPR. MPR values were missing for cases with only one prescription of the statin filled (MPR numerator and denominator=0), or if two or more prescriptions filled, one or more number of days supply was zero or negative (MPR numerator=0 or negative). MPRs with negative or zero values were set to missing.
[b]Frequency and percent of statin use (by statin type) without regard to missing MPR values.

Statin Types and Adherence

Table 4.24 shows the frequency and percent of users of each statin type categorized as non-adherent (MPR<80) or adherent (MPR≥80). A chi-square test showed that there was a significant difference in the proportion of users of each statin type who were adherent or not adherent with their medications ($\chi^2 = 96.4$; df=5; $p<0.0001$).

The table shows that the majority (54.2%, N=27,412) of all statin users were adherent with their medications. The proportion of users of each statin type who were adherent with their medication was highest among lovastatin users (62%, N=2,065) and lowest among fluvastatin users (52.3%, N=796).

Table 4.24: Frequency and Percent of Users of Each Statin Type by Adherence Status

	Atorvastatin N (%)	Fluvastatin N (%)	Lovastatin N (%)	Pravastatin N (%)	Rosuvastatin N (%)	Simvastatin N (%)	Statin Users N (%)
Adherent[a]	13,961 (53.8)	796 (52.3)	2,065 (62.0)	2,929 (53.5)	1,461 (56.0)	6,200 (53.1)	27,412 (54.2)
Non-adherent[b]	11,987 (46.2)	727 (47.7)	1,264 (38.0)	2,543 (46.5)	1,147 (44.0)	5,477 (46.9)	23,145 (45.8)
Total	25,948 (100.0)	1,523 (100.0)	3,329 (100.0)	5,472 (100.0)	2,608 (100.0)	11,677 (100.0)	50,557[c] (100.0)

($\chi^2 = 96.4$; df=5; $p<0.0001$)

[a]MPR≥80%.

[b]MPR<80%.

[c]Total N was less than 58,112 because of missing values for MPR. MPR values were missing for cases with only one prescription of the statin filled (MPR numerator and denominator=0), or if two or more prescriptions filled, one or more number of days supply was zero or negative (MPR numerator=0 or negative). MPRs with negative or zero values were set to missing.

4.3.3.2 Dosage Intensity and Medication Adherence

H_{7b}: The mean medication possession ratio (MPR) will be significantly lower among intensive-dose statin users compared to moderate-dose statin users.

Table 4.25 shows the frequency and percent of intensive-dose and moderate-dose statin users depending on how dosage intensity was defined per study protocol. For this study, intensive-dose statin use was defined as the use of at least one intensive-dose statin at any time during the observation period, while moderate-dose statin use was defined as the use of a moderate-dose statin throughout the observation period. Intensive-dose statins included atorvastatin 40 and 80mg, rosuvastatin 20 and 40mg, and simvastatin 80mg. Moderate-dose statins included atorvastatin 10 and 20mg, rosuvastatin 5 and 10mg, simvastatin 5, 10, 20, and 40mg, and all doses of fluvastatin, pravastatin, and lovastatin.

Table 4.25 shows that the proportions of statin users who were categorized as using intensive-dose statins increased from 5.6% (N=3,272) to 10.7% (N=6,205) when intensive-dose statin use was defined as the use of at least one intensive-dose statin at any time during the observation period rather than the use of an intensive-dose statin at the index date. Nevertheless, the majority (89.3%, N=51,907) of statin users were still prescribed a moderate statin dose.

Table 4.25: Frequency and Percent of Intensive-dose and Moderate-dose Statin Users Based on Definition of Dosage Intensity

Dosage Intensity	N (%)[a]	N (%)[b]
Intensive-dose[c]	3,272 (5.6)	6,205 (10.7)
Moderate-dose[d]	54,840 (94.4)	51,907 (89.3)
Total	58,112 (100.0)	58,112 (100.0)

[a]Dosage intensity defined based on whether subjects received intensive-dose or moderate dose statin at index date (intention-to-treat).
[b]Intensive-dose users defined as receiving at least one intensive-dose statin at any time during the observation period. Moderate-dose users defined as receiving only a moderate-dose statin throughout the observation period.
[c]Intensive-dose statins include atorvastatin 40 and 80mg, rosuvastatin 20 and 40mg, and simvastatin 80mg.
[d]Moderate-dose statins include atorvastatin 10 and 20mg, rosuvastatin 5 and 10mg, simvastatin 5, 10, 20, and 40mg, and all doses of fluvastatin, pravastatin, and lovastatin.

Furthermore, Table 4.26 shows the descriptive statistics of MPR (in percent) for intensive-dose and moderate-dose statin users. Among statin users (N=50,557), an independent samples t-test showed that mean MPR was significantly lower among intensive-dose statin users (70.7., SD=26.4) compared to moderate-dose statin users (75.6, SD=25.1) (t=13.3; df=7,175.8; p<0.0001). [**Conclusion: alternative hypothesis H_{7b} was supported].**

Table 4.26: Descriptive Statistics of Medication Possession Ratio by Statin Dosage Intensity					
Dosage Intensity	**Mean (SD)**	**Median**	**Min**	**Max**	**N (%)**
Intensive-dose[a]	70.7 (26.3)	76.4	0.4	100	5,767 (11.4)
Moderate-dose[b]	75.6 (25.1)	84.0	0.2	100	44,790 (88.6)
Statin users	75.0 (25.3)	83.3	0.2	100	50,557[c] (100.0)
					t-test (t=13.3; df=7,175.8; p<0.0001)

[a]Intensive-dose statins include atorvastatin 40 and 80mg, rosuvastatin 20 and 40mg, and simvastatin 80mg.
[b]Moderate-dose statins include atorvastatin 10 and 20mg, rosuvastatin 5 and 10mg, simvastatin 5, 10, 20, and 40mg, and all doses of fluvastatin, pravastatin, and lovastatin.
[c]Total N was less than 58,112 because of missing values for MPR. MPR values were missing for cases with only one prescription of the statin filled (MPR numerator and denominator=0), or if two or more prescriptions filled, one or more number of days supply was zero or negative (MPR numerator=0 or negative). MPRs with negative or zero values were set to missing.

Dosage Intensity and Adherence

Table 4.27 shows the frequency and percent of intensive-dose and moderate-dose statin users when they were categorized as non-adherent (MPR<80) or adherent (MPR≥80) with their medications. A chi-square test showed that there was a significant difference in the proportion of intensive-dose and moderate-dose statin users who were adherent or not adherent with their medications ($\chi^2 = 176.3$; df=1; p<0.0001). The proportion of moderate-dose statin users who were adherent with their medications (55.3%, N=24,758) was higher compared to the proportion of intensive-dose statin users who were adherent with their medications (46.0%, N=2,654).

Table 4.27: Frequency and Percent of Intensive-dose and Moderate-dose Statin Users by Adherence Status

	Intensive-dose N (%)	Moderate-dose N (%)	Statin Users N (%)
Adherent[a]	2,654 (46.0)	24,758 (55.3)	27,412 (54.2)
Non-adherent[b]	3,113 (54.0)	20,032 (44.7)	23,145 (45.8)
Total	5,767 (100.0)	44,790 (100.0)	50,557[c] (100.0)

($\chi^2 = 176.3$; df=1; $p<0.0001$)

[a]Intensive-dose statins include atorvastatin 40 and 80mg, rosuvastatin 20 and 40mg, and simvastatin 80mg.

[b]Moderate-dose statins include atorvastatin 10 and 20mg, rosuvastatin 5 and 10mg, simvastatin 5, 10, 20, and 40mg, and all doses of fluvastatin, pravastatin, and lovastatin.

[c]Total N was less than 58,112 because of missing values for MPR. MPR values were missing for cases with only one prescription of the statin filled (MPR numerator and denominator=0), or if two or more prescriptions filled, one or more number of days supply was or negative (MPR numerator=0 or negative). MPRs with negative or zero values were set to missing.

4.4 SURVIVAL ANALYSIS (KM Curves and Log-rank Test)

Kaplan-Meier curves (and log-rank tests of the curves) were used to compare the survival time (and the estimated survival probability over time) between statin users and non-statin users (objective 8, hypothesis 8a). Survival time is a continuous variable that was defined as the time between the receipt of the index medication and manifestation of diabetes (for those that had the event), or the time between receipt of the index medication and the end of the study period (for those that reached the end of the study period without manifesting diabetes).

Survival times (and the estimated survival probabilities over time) were also compared among users of each statin type (objective 8, hypothesis 8b), and between intensive-dose statin users and moderate-dose statin users (objective 8, hypothesis 8c). A group with the shorter survival time (or with the shorter survival probability over time, or with its KM survival curve situated below that of its comparator's KM survival curve) may be more likely to have the outcome of interest (diabetes).

The KM survival curves and the log-rank tests of the curves are univariate procedures that compare the survival experience of two or more groups without controlling for any confounding variable. Controlling for confounding variable(s) while comparing the survival experience of two groups was achieved using the Cox proportional hazards regression models discussed in the next section (section 4.5).

Objective 8: To assess whether survival times (i.e., time to diabetes) differed between statin users and non-statin users, among users of each statin type, and between intensive-dose statin users and moderate-dose statin users.

4.4.1 Statin Users and Survival Time

H_{8a}: Statin users will have a shorter survival time compared to non-statin users.

Table 4.28 shows the KM survival estimates and the descriptive statistics of the observed survival times for statin users and non-statin users. The table shows that the proportion of statin users with the event (9.8%, N=5,678) was higher compared to the proportion of non-statin users with the event (3.3%, N=1,915). In addition, the estimated mean survival time (in months) for statin users (16.92, standard error, SE=0.02) was shorter compared to that of non-statin users (17.67, SE=0.01).

Furthermore, Figure 4.3 shows two Kaplan-Meier survival curves comparing the survival probability against time for statin users and non-statin users. The log-rank test comparing the distribution of the two survival curves showed that statin users had a significantly shorter survival probability over time compared to non-statin users (χ^2 = 2,022.8; df=1; $p<0.0001$).

From Figure 4.3, the respective 6-month and 12-month survival probabilities for statin users (95.5% and 91.8%) were lower compared to those for non-statin users (98.7 and 97.3%). At 18-months, the survival probability for statin users fell to 0.89 (i.e., 89% of statin users survived past 18 months without having diabetes) compared to 96.3% of non-statin users that survived past 18 months without having diabetes. Thus, statin users

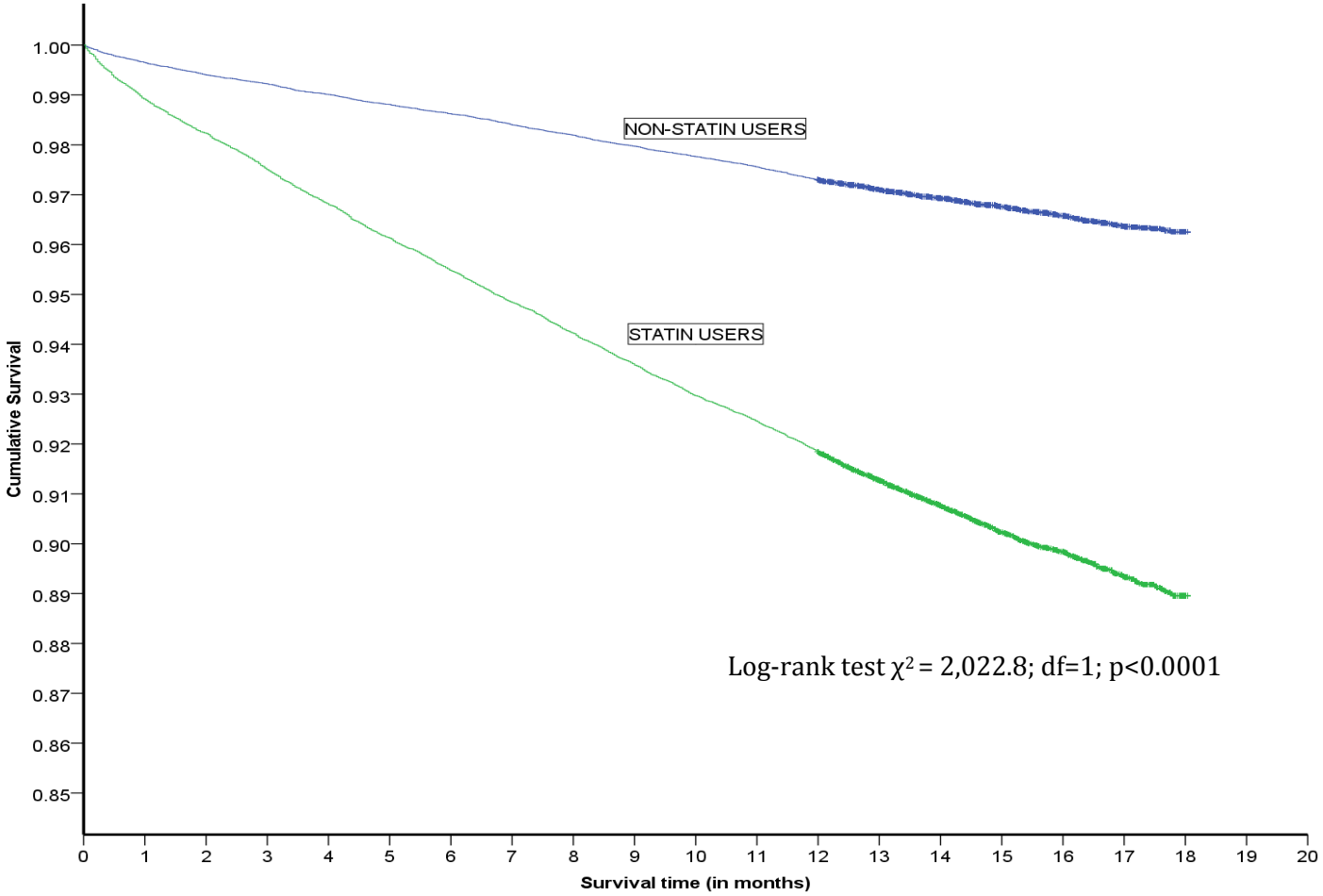
had a shorter survival time (and shorter survival probabilities over time) compared to non-statin users. **[Conclusion: alternative hypothesis H_{8a} was supported].**

Table 4.28: Survival Probability and Mean Survival Time for Statin Users and Non-statin Users

	Statin Users	Non-statin Users
Kaplan-Meier estimates		
Mean (SE) survival time[a]	16.92 (0.02)	17.67 (0.01)
6-month survival probability[b]	95.5	98.7
12-month survival probability[b]	91.8	97.3
18-month survival probability[b]	89.0	96.3
Observed survival time		
Mean (SD)	14.32 (3.27)	14.98 (2.40)
Median	14.82	15.24
Minimum	0.03	0.03
Maximum	18.04	18.04
Number of cases with event (%)	5,678 (9.8)	1,915 (3.3)
Number of cases censored (%)[c]	52,434 (90.2)	56,197 (96.7)
Total number of cases (%)	58,112 (100.0)	58,112 (100.0)

Abbreviations: Standard Error, SE; Standard Deviation, SD.
[a]Kaplan-Meier estimate of the mean survival time and standard error of the population mean survival time (in months).
[b]This is the proportion of subjects that survived (i.e., did not have the event) past the stated month (in percent).
[c]Those censored do not have the event by end of study period.

Figure 4.3: Graph Comparing the Survival Probability Curves of Statin Users and Non-statin Users



ADDENDUM

Incidence Density Rate: Statin users vs. non-statin users

Appendix D shows the weighted and unweighted incidence density rates and the cumulative incidence of diabetes by statin use. From Table D.1 in Appendix D, the unweighted diabetes incidence density rate for statin users (6.82 per 1,000 person-months) was higher compared to that for non-statin users (2.2 per 1,000 person-months). This means that if 1,000 statin users were followed for one month, 6.82 new cases of diabetes will be recorded. This rate is higher compared to the 2.2 new cases of diabetes that will be recorded if 1,000 non-statin users were followed for one month.

4.4.2 Statin Types and Survival Time

$H_{0(8b)}$: There is no significant difference in mean survival time among users of each statin type.

Table 4.29 shows the KM survival estimates and the descriptive statistics of the observed survival times among users of each statin type. The table shows that the proportion of those with the event (i.e., diabetes) was highest among lovastatin users (13.9%, N=564) and lowest among rosuvastatin users (8.1%, N=242). In addition, the estimated mean survival time (in months) was shortest among rosuvastatin users (15.51, SE=0.06) and increased, consecutively, among lovastatin (16.41, SE=0.07), fluvastatin (16.84, SE=0.09), and simvastatin (16.84, SE=0.03) users. Atorvastatin (17.01, SE=0.02) and pravastatin (17.01, SE=0.04) users had the longest estimated mean survival time [Note: having a shorter survival time means getting the event early].

Furthermore, Figure 4.4 shows six Kaplan-Meier survival curves comparing the survival probabilities against time among users of each statin type. The log-rank test comparing the distribution of the six survival curves showed that at least one of the survival curves significantly differed from another ($\chi^2 = 110.8$; df=5; $p<0.0001$).

From Figure 4.4, the proportion of statin users that survived past six months appeared similar for atorvastatin (95.8%), fluvastatin (95.0%), pravastatin (95.8%), rosuvastatin (95.8%), and simvastatin (95.1%) users. In contrast, a lower proportion of lovastatin users (93.0%) survived past six months. Furthermore, the 12-month survival probability appeared significantly lower for lovastatin users (88.5%) compared to

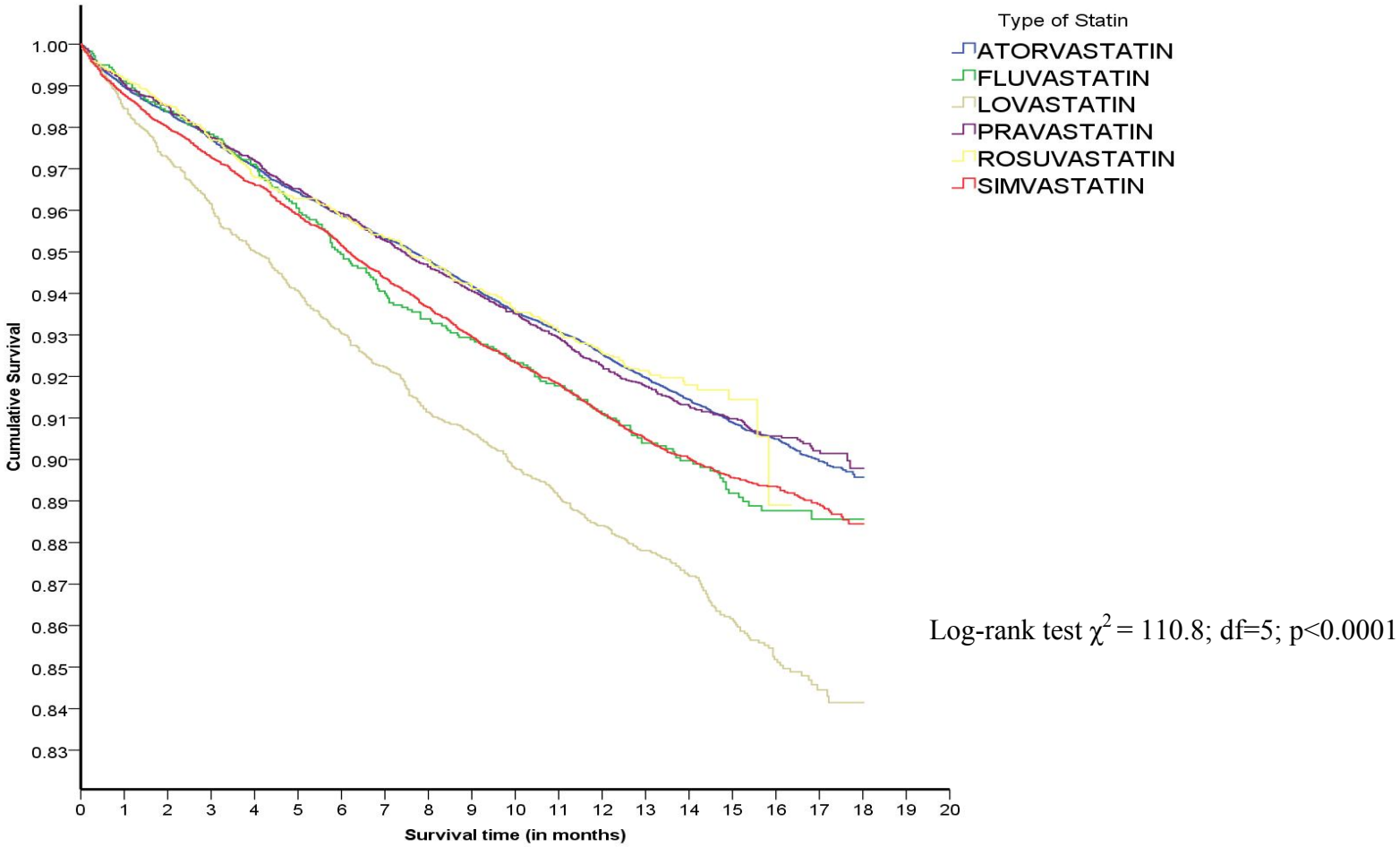
fluvastatin and simvastatin users (91%), pravastatin users (92.3%), and atorvastatin and rosuvastatin users (92.5%). Similarly, at 18-months, the survival probability was lowest for lovastatin users (84.1%) compared to fluvastatin and simvastatin users (88.5%), atorvastatin users (89.6%), and pravastatin users (89.8%). Rosuvastatin users had a survival probability of 88.8% at 16.4 months (their maximally observed survival time). Thus, there was at least one significant difference in mean survival time (and survival probabilities over time) among users of each statin type. [**Conclusion: null hypothesis $H_{0(8b)}$ was rejected].**

Table 4.29: Survival Probability and Mean Survival Times for Statin Types

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Kaplan-Meier estimates						
Mean (SE) survival time[a]	17.01 (0.02)	16.84 (0.09)	16.41 (0.07)	17.01 (0.04)	15.51 (0.06)	16.84 (0.03)
6-month SP[b]	95.8	95.0	93.0	95.8	95.8	95.1
12-month SP[b]	92.5	91.0	88.5	92.3	92.5	91.0
18-month SP[b]	89.6	88.5	84.1	89.8	(88.8)[c]	88.5
Observed survival time						
Mean (SD)	14.41 (3.19)	14.45 (3.38)	13.92 (3.74)	14.62 (3.22)	12.99 (2.53)	14.37 (3.39)
Median	14.95	15.18	14.59	15.24	13.34	15.01
Minimum	0.03	0.03	0.03	0.03	0.03	0.03
Maximum	18.04	18.04	18.04	18.04	16.36	18.04
Events, N (%)	2,690 (9.1)	192 (10.7)	564 (13.9)	587 (9.2)	242 (8.1)	1403 (10.5)
Censored, N (%)[d]	26,784 (90.9)	1,607 (89.3)	3,490 (86.1)	5,796 (90.8)	2,745 (91.9)	12,012 (89.5)
Total, N (%)	29,474 (100.0)	1,799 (100.0)	4,054 (100.0)	6,383 (100.0)	2,987 (100.0)	13,415 (100.0)

Abbreviations: SE, Standard Error; SD, Standard Deviation; SP, Survival Probability.
[a]Kaplan-Meier estimate of the mean survival time (in months) and standard error of the population mean survival time.
[b]This is the proportion of subjects that survived (i.e., did not have the event) past the stated month (in percent).
[c]88.8% of rosuvastatin users survived past 16.36 months (their maximum survival time).
[d]Those censored do not have the event (i.e., diabetes) by end of study period.

Figure 4.4: Graph Comparing the Survival Probability Curves of Different Statin Types



Log-rank test $\chi^2 = 110.8$; df=5; $p<0.0001$

4.4.3 Statin Dosage Intensity and Survival Time

H_{8c}: Intensive-dose statin users will have a shorter survival time compared to moderate-dose statin users.

Table 4.30 shows the KM survival estimates and the descriptive statistics of the observed survival times between intensive-dose statin users and moderate-dose statin users. The table shows that the proportion of intensive-dose statin users with the event (13.4%, N=831) was higher compared to the proportion of moderate-dose statin users with the event (9.3%, N=4,847). In addition, the estimated mean survival time (in months) for intensive-dose statin users (16.51, standard error, SE=0.05) was shorter compared to that of moderate-dose statin users (16.97, SE=0.02).

Furthermore, Figure 4.5 shows two Kaplan-Meier survival curves comparing the survival probability against time for intensive-dose statin users and moderate-dose statin users. The log-rank test comparing the distribution of the two survival curves showed that intensive-dose statin users had a significantly shorter survival probability over time compared to moderate-dose statin users ($\chi^2 = 101.4$; df=1; $p<0.0001$).

From Figure 4.5, the respective 6-month and 12-month survival probabilities for intensive-dose statin users (93.8% and 88.8%) were lower compared to those for moderate-dose statin users (95.7% and 92.2%). At 18-months, the survival probability for intensive-dose statin users fell to 85.2% (i.e., 85.2% of intensive-dose statin users survived past 18 months without having diabetes) compared to 89.5% of moderate-dose statin users that survived past 18 months without having diabetes. Thus, intensive-dose

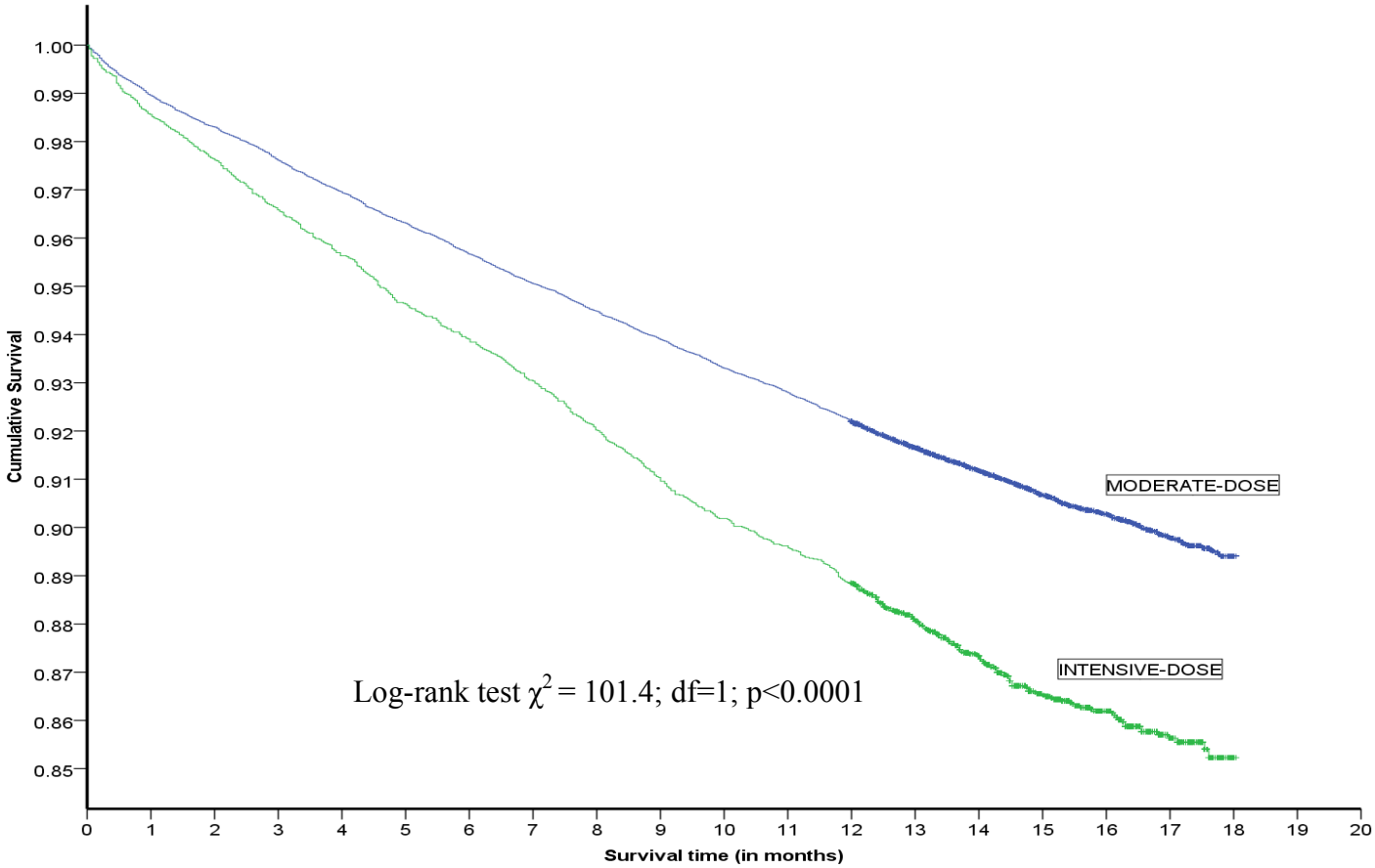
statin users had a shorter survival time (and shorter survival probabilities over time) compared to moderate-dose statin users. [**Conclusion: alternative hypothesis H_{8c} was supported].**

Table 4.30: Survival Probability and Mean Survival Time for Intensive-dose and Moderate-dose Statin Users

	Intensive-dose	Moderate-dose
Kaplan-Meier estimates		
Mean (SE) survival time[a]	16.51 (0.05)	16.97 (0.02)
6-month survival probability[b]	93.8	95.7
12-month survival probability[b]	88.8	92.2
18-month survival probability[b]	85.2	89.5
Observed survival time		
Mean (SD)	14.12 (3.67)	14.34 (3.22)
Median	14.85	14.82
Minimum	0.03	0.03
Maximum	18.04	18.04
Number of cases with event (%)	831 (13.4)	4,847 (9.3)
Number of cases censored (%)[c]	5,374 (86.6)	47,060 (90.7)
Total number of cases (%)	6,205 (100.0)	51,907 (100.0)

Abbreviations: Standard Error, SE; Standard Deviation, SD.
[a]Kaplan-Meier estimate of the mean survival time and standard error of the population mean survival time (in months).
[b]This is the proportion of subjects that survived (i.e., did not have the event) past the stated month (in percent).
[c]Those censored do not have the event by end of study period.

Figure 4.5: Graph Comparing the Survival Probability Curves of Intensive-Dose and Moderate-Dose Statin Users



ADDENDUM

Incidence Density Rate: Intensive-dose statin users vs. moderate-dose statin users

Appendix D shows the weighted and unweighted incidence density rate and cumulative incidence of diabetes by statin use. From Table D.1, the unweighted diabetes incidence density rate for intensive-dose statin users (9.48 per 1,000 person-months) was higher compared to that for moderate-dose statin users (6.51 per 1,000 person-months). This means that if 1,000 intensive-dose statin users were followed for one month, 9.48 new cases of diabetes will be recorded. This rate is higher compared to the 6.51 new cases of diabetes that will be recorded if 1,000 moderate-dose statin users were followed for one month.

4.5 SURVIVAL ANALYSIS (Cox Regression)

The preceding section (section 4.4) compared, among other things, the survival experience of statin users and non-statin users (using KM curves and log-rank test) without controlling for confounding variables that may increase the risk of diabetes in one group versus the other. Because of the need to control for confounding factors such as demographic (age and gender) and clinical characteristics (hyperlipidemia, obesity, hypertension, use of diabetogenic medications, and CCI score), this section utilized the Cox proportional hazards regression (or the Cox regression) to compare the hazard of diabetes between statin users and non-statin users (objective 9, hypothesis 9a), between users of each statin type and non-statin users (objective 9, hypothesis 9b-g), and between intensive-dose statin users and moderate-dose statin users (objective 10, hypothesis 10).

The hazard ratio (HR) gives an estimate of the hazard of diabetes in the active group (i.e., statin users and users of each statin type) relative to that of the reference group (i.e., non-statin users). HRs greater than 1.0 indicate that the hazard of diabetes (or the risk of diabetes) among the active group is higher than the hazard of diabetes among the reference group.

In addition to the main Cox regression models examining the association of statin use and incidence of diabetes while controlling for all covariates, three additional sensitivity analyses were carried out (on each original Cox regression model) to examine how the hazard ratios were influenced by: (i) controlling for time-dependent covariates (i.e., independent variables that violated the proportionality of hazards assumption), (ii)

not controlling for the obesity variable in the model (due to low prevalence of obesity among the study population compared to that of the adult US population), and (iii) not controlling for any of the covariates (i.e., unadjusted models).

The hazard ratios (and 99% confidence intervals of the HRs) of the sensitivity analyses results were presented alongside those of the main results. Appendices C, E, and F also give a visual summary of the sensitivity analyses of the hazard ratios when significant time-dependent covariates were controlled for, when none of the covariates were controlled for, and when obesity was not controlled for, respectively.

Objective 9: To assess whether survival times differed between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use [i.e., number of prescriptions for all diabetogenic medications], and CCI score).

4.5.1 Statin Users

H_{9a}: Statin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for statin users (16.92, SE=0.02) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.31 shows the results of the Cox regression model comparing survival time between statin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=4,036.8; df=8; p<0.0001). This means that at least

one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, statin use was significantly associated with increased risk of incident diabetes mellitus [HR=2.752; 99% C.I.=2.535 – 2.987; p<0.0001]. In other words, the hazard of incident diabetes for statin users was 2.752 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., gender, hyperlipidemia, hypertension, and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for statin users increased, and was 2.812 times those of non-statin users [HR=2.812; 99% C.I.=2.590 – 3.052; p<0.0001]. However, when the obesity variable was not controlled for in a separate model, the hazard ratio comparing statin users to non-statin users increased marginally and remained significant [HR=2.765; 99% C.I.=2.548 – 3.002; p<0.0001]. [**Conclusion: alternative hypothesis H_{9a} was supported].**

Table 4.31: Cox Regression Model Comparing Survival Time between Statin Users and Non-statin Users while Controlling for Covariates (N=116,224)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Statin[a]	1.012	0.032	1009.438	**p<0.0001**	**2.752**	**2.535**	**2.987**
Age	0.032	0.001	525.357	p<0.0001	1.033	1.029	1.036
Gender: Male[b]	-0.064	0.023	7.675	0.006	0.938	0.884	0.996
Hyperlipidemia	-0.423	0.026	260.766	p<0.0001	0.655	0.612	0.701
Obesity	0.573	0.101	31.929	p<0.0001	1.773	1.366	2.302
Hypertension	0.344	0.027	164.668	p<0.0001	1.410	1.316	1.511
Diabetogenic medications	-0.049	0.002	555.108	p<0.0001	0.953	0.948	0.958
CCI score	0.131	0.009	201.689	p<0.0001	1.140	1.114	1.168

Model Parameters: χ^2=4,036.8; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., gender, hyperlipidemia, hypertension, and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing statin users to non-statin users increased and remained significant [HR=2.812; 99% C.I.: 2.590 – 3.052; p<0.0001].

Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing statin users to non-statin users increased and remained significant [HR=3.089; 99% C.I.=2.886 – 3.307; p<0.0001].

Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing statin users to non-statin users increased marginally and remained significant [HR=2.765; 99% C.I.=2.548 – 3.002; p<0.0001].

4.5.2 Atorvastatin

H_{9b}: Atorvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for atorvastatin users (17.01, SE=0.02) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.32 shows the results of the Cox regression model comparing survival time between atorvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=2,637.1; df=8; p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, atorvastatin use was significantly associated with increased risk of incident diabetes mellitus [HR=2.425; 99% C.I.=2.200 – 2.673; p<0.0001]. In other words, the hazard of incident diabetes for atorvastatin users was 2.425 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., gender, hyperlipidemia, and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for atorvastatin users increased, and was 2.474 times those of non-statin users [HR=2.474; 99% C.I.=2.244 – 2.727; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing atorvastatin users to non-statin users increased marginally and remained significant

[HR=2.430; 99% C.I.=2.204 – 2.678; p<0.0001]. [**Conclusion: alternative hypothesis H_{9b} was supported].**

Table 4.32: Cox Regression Model Comparing Survival Time between Atorvastatin Users and Non-statin Users while Controlling for Covariates (N=87,586)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Atorvastatin[a]	0.886	0.038	548.135	**p<0.0001**	**2.425**	**2.200**	**2.673**
Age	0.033	0.002	402.828	p<0.0001	1.034	1.029	1.038
Gender: Male[b]	-0.061	0.030	4.226	0.04	0.941	0.872	1.016
Hyperlipidemia	-0.387	0.036	113.303	p<0.0001	0.679	0.618	0.746
Obesity	0.365	0.157	5.396	0.02	1.441	0.961	2.159
Hypertension	0.409	0.037	122.561	p<0.0001	1.505	1.369	1.656
Diabetogenic medications	-0.044	0.003	238.879	p<0.0001	0.957	0.950	0.964
CCI score	0.152	0.012	155.046	p<0.0001	1.164	1.128	1.201

Model Parameters: χ^2=2,637.1; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., gender, hyperlipidemia, and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing atorvastatin users to non-statin users increased and remained significant [HR=2.474; 99% C.I.=2.244 – 2.727; p<0.0001].

Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing atorvastatin users to non-statin users increased and remained significant [HR=2.871; 99% C.I.=2.658 – 3.101; p<0.0001].

Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing atorvastatin users to non-statin users increased marginally and remained significant [HR=2.430; 99% C.I.=2.204 – 2.678; p<0.0001].

4.5.3 Fluvastatin

H_{9c}: Fluvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for fluvastatin users (16.84, SE=0.09) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.33 shows the results of the Cox regression model comparing survival time between fluvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=855.2; df=8; p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, fluvastatin use was significantly associated with increased risk of incident diabetes mellitus [HR=2.064; 99% C.I.=1.647 – 2.586; p<0.0001]. In other words, the hazard of incident diabetes for fluvastatin users was 2.064 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., age and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for fluvastatin users increased, and was 2.072 times those of non-statin users [HR=2.072; 99% C.I.=1.653 – 2.599; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing fluvastatin users to non-statin users increased marginally and remained significant [HR=2.067; 99%

C.I.=1.649 – 2.589; p<0.0001]. [**Conclusion: alternative hypothesis H_{9c} was supported].**

Table 4.33: Cox Regression Model Comparing Survival Time between Fluvastatin Users and Non-statin Users while Controlling for Covariates (N=59,911)

	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Fluvastatin[a]	0.725	0.088	68.452	**p<0.0001**	**2.064**	**1.647**	**2.586**
Age	0.036	0.002	305.844	p<0.0001	1.037	1.032	1.043
Gender: Male[b]	-0.044	0.044	1.006	0.316	0.957	0.855	1.071
Hyperlipidemia	-0.041	0.073	0.312	0.576	0.960	0.795	1.159
Obesity	0.202	0.334	0.364	0.546	1.224	0.517	2.895
Hypertension	0.653	0.072	83.119	p<0.0001	1.921	1.598	2.310
Diabetogenic medications	-0.032	0.007	23.627	p<0.0001	0.968	0.952	0.985
CCI score	0.167	0.027	38.321	p<0.0001	1.182	1.103	1.267

Model Parameters: χ^2=855.2; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., age and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing fluvastatin users to non-statin users increased and remained significant [HR=2.072; 99% C.I.=1.653 – 2.599; p<0.0001].

Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing fluvastatin users to non-statin users increased and remained significant [HR=3.354; 99% C.I.=2.760 – 4.076; p<0.0001].

Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing fluvastatin users to non-statin users increased marginally and remained significant [HR=2.067; 99% C.I.=1.649 – 2.589; p<0.0001].

4.5.4 Lovastatin

H_{9d}: Lovastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for lovastatin users (16.41, SE=0.02) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.34 shows the results of the Cox regression model comparing survival time between lovastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,896; df=8; p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, lovastatin use was significantly associated with increased risk of incident diabetes mellitus [HR=3.413; 99% C.I.=2.949 – 3.951; p<0.0001]. In other words, the hazard of incident diabetes for lovastatin users was 3.413 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., gender and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for lovastatin users increased, and was 3.501 times those of non-statin users [HR=3.501; 99% C.I.=3.025 – 4.051; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing lovastatin users to non-statin users increased marginally and remained significant [HR=3.455; 99%

C.I.=2.988 – 3.997; p<0.0001]. [**Conclusion: alternative hypothesis H_{9d} was supported].**

Table 4.34: Cox Regression Model Comparing Survival Time between Lovastatin Users and Non-statin Users while Controlling for Covariates (N=62,166)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Lovastatin[a]	1.228	0.057	466.996	**p<0.0001**	**3.413**	**2.949**	**3.951**
Age	0.037	0.002	344.885	p<0.0001	1.038	1.033	1.043
Gender: Male[b]	-0.053	0.040	1.701	0.192	0.949	0.855	1.053
Hyperlipidemia	-0.175	0.064	7.442	0.006	0.839	0.712	0.990
Obesity	0.462	0.185	6.208	0.013	1.587	0.985	2.558
Hypertension	0.600	0.062	92.797	p<0.0001	1.821	1.552	2.138
Diabetogenic medications	-0.057	0.006	105.323	p<0.0001	0.944	0.931	0.958
CCI score	0.154	0.024	41.181	p<0.0001	1.166	1.097	1.241

Model Parameters: χ^2=1,896.4; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., gender and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing lovastatin users to non-statin users increased and remained significant [HR=3.501; 99% C.I.=3.025 – 4.051; p<0.0001].
Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing lovastatin users to non-statin users increased and remained significant [HR=4.521; 99% C.I.=3.996 – 5.115; p<0.0001].
Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing lovastatin users to non-statin users increased marginally and remained significant [HR=3.455; 99% C.I.=2.988 – 3.997; p<0.0001].

4.5.5 Pravastatin

H_{9e}: Pravastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for pravastatin users (17.01, SE=0.04) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.35 shows the results of the Cox regression model comparing survival time between pravastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,334.7; df=8; p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, pravastatin use was significantly associated with increased risk of incident diabetes mellitus [HR=1.889; 99% C.I.=1.620 – 2.202; p<0.0001]. In other words, the hazard of incident diabetes for pravastatin users was 1.889 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., gender, hyperlipidemia, and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for pravastatin users increased, and was 1.905 times those of non-statin users [HR=1.905; 99% C.I.=1.633 – 2.222; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing pravastatin users to non-statin users increased marginally and remained significant

[HR=1.890; 99% C.I.=1.621 – 2.203; p<0.0001]. [**Conclusion: alternative hypothesis H_{9e} was supported].**

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Table 4.35: Cox Regression Model Comparing Survival Time between Pravastatin Users and Non-statin Users while Controlling for Covariates (N=64,495)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Pravastatin[a]	0.636	0.060	113.865	**p<0.0001**	**1.889**	**1.620**	**2.202**
Age	0.037	0.002	349.844	p<0.0001	1.038	1.033	1.044
Gender: Male[b]	-0.061	0.040	2.304	0.129	0.941	0.848	1.043
Hyperlipidemia	-0.139	0.060	5.313	0.021	0.870	0.745	1.016
Obesity	0.185	0.290	0.406	0.524	1.203	0.570	2.536
Hypertension	0.629	0.059	112.723	p<0.0001	1.876	1.610	2.185
Diabetogenic medications	-0.043	0.005	71.124	p<0.0001	0.958	0.945	0.971
CCI score	0.172	0.020	74.894	p<0.0001	1.187	1.128	1.249

Model Parameters: χ^2=1,334.7; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., gender, hyperlipidemia, and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing pravastatin users to non-statin users increased and remained significant [HR=1.905; 99% C.I.=1.633 – 2.222; p<0.0001].

Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing pravastatin users to non-statin users increased and remained significant [HR=2.859; 99% C.I.=2.532 – 3.228; p<0.0001].

Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing pravastatin users to non-statin users increased marginally and remained significant [HR=1.890; 99% C.I.=1.621 – 2.203; p<0.0001].

4.5.6 Rosuvastatin

H_{9f}: Rosuvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for rosuvastatin users (15.51, SE=0.06) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.36 shows the results of the Cox regression model comparing survival time between rosuvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=926.6; df=8; p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, rosuvastatin use was significantly associated with increased risk of incident diabetes mellitus [HR=1.615; 99% C.I.=1.307 – 1.996; p<0.0001]. In other words, the hazard of incident diabetes for rosuvastatin users was 1.615 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., gender and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for rosuvastatin users increased, and was 1.665 times those of non-statin users [HR=1.665; 99% C.I.=1.348 – 2.057; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing rosuvastatin users to non-statin users increased marginally and remained significant [HR=1.621; 99%

C.I.=1.311 – 2.003; p<0.0001]. [**Conclusion: alternative hypothesis H_{9f} was supported].**

Table 4.36: Cox Regression Model Comparing Survival Time between Rosuvastatin Users and Non-statin Users while Controlling for Covariates (N=61,099)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Rosuvastatin[a]	0.480	0.082	34.043	**p<0.0001**	**1.615**	**1.307**	**1.996**
Age	0.036	0.002	303.255	p<0.0001	1.037	1.031	1.042
Gender: Male[b]	-0.062	0.043	2.057	0.152	0.940	0.841	1.051
Hyperlipidemia	-0.006	0.070	0.008	0.930	0.994	0.829	1.191
Obesity	0.571	0.278	4.205	0.040	1.770	0.864	3.627
Hypertension	0.725	0.068	113.620	p<0.0001	2.064	1.733	2.459
Diabetogenic medications	-0.030	0.006	23.941	p<0.0001	0.971	0.955	0.986
CCI score	0.187	0.024	61.725	p<0.0001	1.206	1.134	1.282

Model Parameters: χ^2=926.6; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., gender and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing rosuvastatin users to non-statin users increased and remained significant [HR=1.665; 99% C.I.=1.348 – 2.057; p<0.0001].
Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing rosuvastatin users to non-statin users increased and remained significant [HR=2.777; 99% C.I.=2.328 – 3.313; p<0.0001].
Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing rosuvastatin users to non-statin users increased marginally and remained significant [HR=1.621; 99% C.I.=1.311 – 2.003; p<0.0001].

4.5.7 Simvastatin

H_{9g}: Simvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for simvastatin users (16.84, SE=0.03) was shorter compared to that of non-statin users (17.67, SE=0.01).

Table 4.37 shows the results of the Cox regression model comparing survival time between simvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=2,283.0; df=8; p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to no statin use, and controlling for covariates, simvastatin use was significantly associated with increased risk of incident diabetes mellitus [HR=2.567; 99% C.I.=2.284 – 2.884; p<0.0001]. In other words, the hazard of incident diabetes for simvastatin users was 2.567 times the hazard of incident diabetes for non-statin users. When significant time-dependent covariates specific to this model (i.e., hyperlipidemia and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for simvastatin users increased, and was 2.622 times those of non-statin users [HR=2.622; 99% C.I.=2.334 – 2.946; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing simvastatin users to non-statin users increased marginally and remained significant [HR=2.574; 99%

C.I.=2.291 – 2.892; p<0.0001]. [**Conclusion: alternative hypothesis H_{9g} was supported].**

Table 4.37: Cox Regression Model Comparing Survival Time between Simvastatin Users and Non-statin Users while Controlling for Covariates (N=71,527)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Simvastatin[a]	0.943	0.045	433.518	**p<0.0001**	**2.567**	**2.284**	**2.884**
Age	0.036	0.002	392.325	p<0.0001	1.037	1.032	1.042
Gender: Male[b]	-0.011	0.035	0.101	0.75	0.989	0.904	1.082
Hyperlipidemia	-0.295	0.047	39.105	p<0.0001	0.745	0.660	0.841
Obesity	0.655	0.187	12.309	p<0.0001	1.926	1.190	3.116
Hypertension	0.478	0.047	104.066	p<0.0001	1.612	1.429	1.819
Diabetogenic medications	-0.049	0.004	168.956	p<0.0001	0.952	0.943	0.962
CCI score	0.128	0.015	70.020	p<0.0001	1.136	1.092	1.182

Model Parameters: χ^2=2,283.0; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., hyperlipidemia and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing simvastatin users to non-statin users increased and remained significant [HR=2.622; 99% C.I.=2.334 – 2.946; p<0.0001].
Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing simvastatin users to non-statin users increased and remained significant [HR=3.299; 99% C.I.=3.014 – 3.612; p<0.0001].
Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing simvastatin users to non-statin users increased marginally and remained significant [HR=2.574; 99% C.I.=2.291 – 2.892; p<0.0001].

4.5.8 Dosage Intensity

Objective 10: To assess whether survival times differed between intensive-dose statin users and moderate-dose statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, CCI score, and medication adherence).

H_{10}: Intensive-dose statin users will have a significantly shorter survival time compared to moderate-dose statin users while controlling for age, gender, and clinical covariates.

The estimated mean survival time (in months) for intensive-dose statin users (16.51, SE=0.05) was shorter compared to that of moderate-dose statin users (16.97, SE=0.02).

Table 4.38 shows the results of the Cox regression model comparing survival time between intensive-dose statin users and moderate-dose statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,286.7; df=9, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (survival time).

Compared to moderate-dose statin use, and controlling for covariates, intensive-dose statin use was significantly associated with increased risk of incident diabetes mellitus [HR=1.525; 99% C.I.=1.378 – 1.686; p<0.0001]. In other words, the hazard of incident diabetes for intensive-dose statin users was 1.525 times the hazard of incident diabetes for moderate-dose statin users. When significant time-dependent covariates

specific to this model (i.e., age, gender, hyperlipidemia, hypertension, and diabetogenic medications) were controlled for in a separate model, the hazard of incident diabetes for intensive-dose statin users increased, and was 1.540 times those of moderate-dose statin users [HR=1.540; 99% C.I.=1.393 – 1.704; p<0.0001]. However, when obesity was not controlled for in another separate model, the hazard ratio comparing intensive-dose statin users to moderate-dose statin users increased marginally and remained significant [HR=1.526; 99% C.I.=1.379 – 1.688; p<0.0001]. [**Conclusion: alternative hypothesis H_{10} was supported].**

Table 4.39 is a summary of Tables 4.31 – 4.38 that gives a visual comparison of the strength of association (i.e., hazard ratios) of statin use and incident diabetes.

Table 4.38: Cox Regression Model Comparing Survival Time between Intensive-dose Statin Users and Moderate-dose Statin Users while Controlling for Covariates (N=50,557)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Dosage intensity: Intensive-dose[a]	0.422	0.039	116.165	**p<0.0001**	**1.525**	**1.378**	**1.686**
Age	0.026	0.002	156.593	p<0.0001	1.026	1.021	1.031
Gender: Male[b]	-0.104	0.029	13.196	p<0.0001	0.901	0.837	0.970
Hyperlipidemia	-0.500	0.029	297.859	p<0.0001	0.607	0.563	0.654
Obesity	0.584	0.113	26.814	p<0.0001	1.794	1.341	2.399
Hypertension	0.287	0.030	92.918	p<0.0001	1.333	1.234	1.439
Diabetogenic medications	-0.053	0.002	547.188	p<0.0001	0.948	0.943	0.954
CCI score	0.119	0.010	128.276	p<0.0001	1.126	1.096	1.157
Adherence (MPR)[c]	0.024	0.056	0.183	0.669	1.024	0.887	1.183

Model Parameters: χ^2=1,286.7; df=9, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Moderate-dose statin users.

[b]Reference=Female.

[c]Adherence evaluated using the medication possession ratio, MPR.

Sensitivity Analysis I: When significant time-dependent covariates specific to this model (i.e., age, gender, hyperlipidemia, hypertension, and diabetogenic medications) were controlled for in a separate model, the hazard ratio comparing intensive-dose statin users to moderate-dose statin users increased and remained significant [HR=1.540; 99% C.I.=1.393 – 1.704; p<0.0001].

Sensitivity Analysis II: When none of the model covariates were controlled for in a separate model, the hazard ratio comparing intensive-dose statin users to moderate-dose statin users decreased and remained significant [HR=1.456; 99% C.I.=1.322 – 1.604; p<0.0001].

Sensitivity Analysis III: When obesity was not controlled for in another separate model, the hazard ratio comparing intensive-dose statin users to moderate-dose statin users increased marginally and remained significant [HR=1.526; 99% C.I.=1.379 – 1.688; p<0.0001].

Table 4.39: A Summary of Tables 4.31 – 4.38 Showing the Statistical Significance of the Hazard Ratios of the Association between Statin Use and Incident Diabetes (Cox Regression)

	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Hazard Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	1.012	0.032	1009.438	p<0.0001	**2.752**	2.535	2.987
Atorvastatin[a,c]	0.886	0.038	548.135	p<0.0001	**2.425**	2.200	2.673
Fluvastatin[a,c]	0.725	0.088	68.452	p<0.0001	**2.064**	1.647	2.586
Lovastatin[a,c]	1.228	0.057	466.996	p<0.0001	**3.413**	2.949	3.951
Pravastatin[a,c]	0.636	0.060	113.865	p<0.0001	**1.889**	1.620	2.202
Rosuvastatin[a,c]	0.480	0.082	34.043	p<0.0001	**1.615**	1.307	1.996
Simvastatin[a,c]	0.943	0.045	433.518	p<0.0001	**2.567**	2.284	2.884
Intensive-dose statin[b,d]	0.422	0.039	116.165	p<0.0001	**1.525**	1.378	1.686

[Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Moderate-dose statin.

[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.

[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

4.6 LOGISTIC REGRESSION ANALYSIS

In the preceding section (i.e., section 4.5), two groups were compared on a dependent variable that was continuous in nature (i.e., survival time). The purpose of this section was to conduct an alternate analysis, using logistic regression, when the dependent variable is dichotomous in nature (i.e., presence or absence of incident diabetes). The magnitude of the risk ratios (i.e., hazard ratios) obtained from the Cox regression analyses and those of the logistic regression analyses (i.e., odds ratios) were then compared for consistency. Like the hazard ratio which compares the hazard of diabetes in the active group versus the hazard of diabetes in the reference group, the odds ratio (OR) also compares the odds of diabetes in the active group (i.e., statin users and users of each statin type) versus the odds of diabetes in the reference group (i.e., non-statin users). ORs greater than 1.0 indicate that the odds of diabetes (or the risk of diabetes) among the active group is higher than the odds of diabetes among the reference group.

Thus, the aim of this logistic regression section, while controlling for demographic and clinical covariates, was to compare the incidence of diabetes between statin users and non-statin users (objective 11, hypothesis 11b), between users of each statin type and non-statin users (objective 11, hypotheses 11c-h), and between intensive-dose statin users and moderate-dose statin users (objective 12, hypothesis 12).

In addition to the main logistic regression models examining the association of statin use and incidence of diabetes while controlling for all covariates, two additional

sensitivity analyses were carried out (on each original logistic regression model) to examine how the odds ratios were influenced by: (i) not controlling for the obesity variable in the model (due to low prevalence of obesity among the study population compared to that of the adult US population), and (ii) not controlling for any of the covariates (i.e., unadjusted models). The odds ratios (and 99% confidence intervals of the ORs) of the sensitivity analyses results were then presented alongside those of the main results. Appendices E and F also give a visual summary of the sensitivity analyses of the odds ratios when none of the covariates were controlled for, and when obesity was not controlled for, respectively.

Objective 11: To assess whether incidence of diabetes differed between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score).

4.6.1 Statin Users

H_{11a}: The proportion of statin users with incident diabetes will be significantly higher compared to that of non-statin users.

Table 4.40 shows incident diabetes distribution for statin users and non-statin users. Among the study population (N=116,224), 6.5% (or N=7,593) had incident diabetes. An unadjusted chi-square analysis showed that the proportion of statin users with incident diabetes (9.8%, N=5,678) was higher compared to the proportion of non-

statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 1,995.2; df=1; p<0.0001).

[**Conclusion: alternative hypothesis H_{11a} was supported].**

Table 4.40: Frequency and Percent of Statin Users and Non-statin Users by Incident Diabetes

Diabetes	Statin Users N (%)	Non-statin Users N (%)	Study Population N (%)
Yes	5,678 (9.8)	1,915 (3.3)	7,593 (6.5)
No	52,434 (90.2)	56,197 (96.7)	108,631 (93.5)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)

χ^2 = 1,995.2; df=1; p<0.0001

H_{11b}: The proportion of statin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Alternative hypothesis 11a was accepted and showed that the proportion of statin users with incident diabetes was higher than the proportion of non-statin users with incident diabetes. In addition, Table 4.41 shows the results of the binary logistic regression model comparing the odds of incident diabetes between statin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=3,775.2; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.216) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for all covariates, statin use was significantly associated with increased risk of incident diabetes mellitus [OR=2.824; 99% C.I.=2.594 – 3.074; p<0.0001]. In other words, the odds of incident diabetes for statin users were 2.824 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing statin users to non-statin users increased marginally and remained significant [OR=2.838; 99% C.I.=2.607 – 3.089; p<0.0001]. [**Conclusion: alternative hypothesis H_{11b} was supported].**

Table 4.41: Logistic Regression Model Comparing Incident Diabetes between Statin Users and Non-statin Users while Controlling for Covariates (N=116,224)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Statin[a]	1.038	0.033	993.897	**p<0.0001**	**2.824**	**2.594**	**3.074**
Age	0.033	0.001	531.678	p<0.0001	1.034	1.030	1.038
Gender: Male[b]	-0.071	0.024	8.437	0.004	0.932	0.875	.992
Hyperlipidemia	-0.451	0.028	264.644	p<0.0001	0.637	0.593	.684
Obesity	0.597	0.111	28.773	p<0.0001	1.817	1.364	2.420
Hypertension	0.359	0.029	157.286	p<0.0001	1.431	1.330	1.541
Diabetogenic medications	-0.049	0.002	524.305	p<0.0001	0.952	0.947	.957
CCI score	0.148	0.011	185.437	p<0.0001	1.160	1.128	1.192
Constant	-4.740	0.070	4,553.366	p<0.0001	0.009	-	-

Model Parameters: χ^2=3,775.2; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing statin users to non-statin users increased and remained significant [OR=3.178; 99% C.I.=2.963 – 3.408; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing statin users to non-statin users increased marginally and remained significant [OR=2.838; 99% C.I.=2.607 – 3.089; p<0.0001].

4.6.2 Atorvastatin

H_{11b}: The proportion of atorvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Table 4.42 shows incident diabetes distribution for atorvastatin users and non-statin users. An unadjusted chi-square analysis showed that the proportion of atorvastatin users with incident diabetes (9.1%, N=2,690) was higher compared to the proportion of non-statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 1,334.9; df=1; p<0.0001).

Table 4.42: Frequency and Percent of Atorvastatin Users and Non-statin Users with Incident Diabetes

Diabetes	Atorvastatin Users N (%)	Non-statin Users N (%)	Total N (%)
Yes	2,690 (9.1)	1,915 (3.3)	4,605 (5.3)
No	26,784 (90.9)	56,197 (96.7)	82,981 (94.7)
Total	29,474 (100.0)	58,112 (100.0)	87,586 (100.0)

χ^2=1,334.9; df=1; p<0.0001

Table 4.43 shows the results of the binary logistic regression model comparing the odds of incident diabetes between atorvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=2,249.7; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.257) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for covariates, atorvastatin use was significantly associated with increased risk of incident diabetes mellitus [OR=2.485; 99% C.I.=2.246 – 2.749; $p<0.0001$]. In other words, the odds of incident diabetes for atorvastatin users were 2.485 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing atorvastatin users to non-statin users increased marginally and remained significant [OR=2.490; 99% C.I.=2.251 – 2.755; $p<0.0001$]. [**Conclusion: alternative hypothesis H_{11c} was supported].**

Table 4.43: Logistic Regression Model Comparing Incident Diabetes between Atorvastatin Users and Non-statin Users while Controlling for Covariates (N=87,586)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Atorvastatin[a]	0.910	0.039	538.842	**p<0.0001**	**2.485**	**2.246**	**2.749**
Age	0.034	0.002	406.603	p<0.0001	1.035	1.030	1.040
Gender: Male[b]	-0.068	0.031	4.793	0.029	0.935	0.863	1.012
Hyperlipidemia	-0.412	0.038	115.884	p<0.0001	0.662	0.600	0.731
Obesity	0.368	0.168	4.800	0.028	1.445	0.937	2.229
Hypertension	0.423	0.039	116.808	p<0.0001	1.527	1.381	1.689
Diabetogenic medications	-0.044	0.003	223.539	p<0.0001	0.957	0.950	0.964
CCI score	0.169	0.014	137.994	p<0.0001	1.184	1.141	1.229
Constant	-4.793	0.081	3,470.367	p<0.0001	0.008	-	-

Model Parameters: χ^2=2,249.7; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing atorvastatin users to non-statin users increased and remained significant [OR=2.947; 99% C.I.=2.722 – 3.191; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing atorvastatin users to non-statin users increased marginally and remained significant [OR=2.490; 99% C.I.=2.251 – 2.755; p<0.0001].

4.6.3 Fluvastatin

H_{11d}: The proportion of fluvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Table 4.44 shows incident diabetes distribution for fluvastatin users and non-statin users. An unadjusted chi-square analysis showed that the proportion of fluvastatin users with incident diabetes (10.7%, N=192) was higher compared to the proportion of non-statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 279.9; df=1; p<0.0001).

Table 4.44: Frequency and Percent of Fluvastatin Users and Non-statin Users with Incident Diabetes

Diabetes	Fluvastatin Users N (%)	Non-statin Users N (%)	Total N (%)
Yes	192 (10.7)	1,915 (3.3)	2,107 (3.5)
No	1,607 (89.3)	56,197 (96.7)	57,804 (96.5)
Total	1,799 (100.0)	58,112 (100.0)	59,911 (100.0)

χ^2=279.9; df=1; p<0.0001

Table 4.45 shows the results of the binary logistic regression model comparing the odds of incident diabetes between fluvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=683.7; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.068) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for covariates, fluvastatin use was significantly associated with increased risk of incident diabetes mellitus [OR=2.161; 99% C.I.=1.704 – 2.742; p<0.0001]. In other words, the odds of incident diabetes for fluvastatin users were 2.161 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing fluvastatin users to non-statin users increased marginally and remained significant [OR=2.164; 99% C.I.=1.706 – 2.745; p<0.0001]. [**Conclusion: alternative hypothesis H_{11d} was supported].**

Table 4.45: Logistic Regression Model Comparing Incident Diabetes between Fluvastatin Users and Non-statin Users while Controlling for Covariates (N=59,911)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Fluvastatin[a]	0.771	0.092	69.572	**p<0.0001**	**2.161**	**1.704**	**2.742**
Age	0.037	0.002	304.870	p<0.0001	1.038	1.032	1.044
Gender: Male[b]	-0.050	0.045	1.238	0.266	0.951	0.847	1.068
Hyperlipidemia	-0.050	0.076	0.428	0.513	0.952	0.782	1.157
Obesity	0.211	0.347	0.368	0.544	1.235	0.505	3.020
Hypertension	0.670	0.075	80.523	p<0.0001	1.955	1.613	2.370
Diabetogenic medications	-0.031	0.007	21.057	p<0.0001	0.969	0.952	0.986
CCI score	0.182	0.030	36.504	p<0.0001	1.200	1.110	1.296
Constant	-4.982	0.100	2,492.170	p<0.0001	0.007	-	-

Model Parameters: χ^2=683.7; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing fluvastatin users to non-statin users increased and remained significant [OR=3.506; 99% C.I.=2.855 – 4.306; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing fluvastatin users to non-statin users increased marginally and remained significant [OR=2.164; 99% C.I.=1.706 – 2.745; p<0.0001].

4.6.4 Lovastatin

H_{11e}: The proportion of lovastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Table 4.46 shows incident diabetes distribution for lovastatin users and non-statin users. An unadjusted chi-square analysis showed that the proportion of lovastatin users with incident diabetes (13.9%, N=564) was higher compared to the proportion of non-statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 1,115.7; df=1; p<0.0001).

Table 4.46: Frequency and Percent of Lovastatin Users and Non-statin Users with Incident Diabetes

Diabetes	Lovastatin Users N (%)	Non-statin Users N (%)	Total N (%)
Yes	564 (13.9)	1,915 (3.3)	2,479 (4.0)
No	3,490 (86.1)	56,197 (96.7)	59,687 (96.0)
Total	4,054 (100.0)	58,112 (100.0)	62,166 (100.0)

χ^2=1,115.7; df=1; p<0.0001

Table 4.47 shows the results of the binary logistic regression model comparing the odds of incident diabetes between lovastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,322.8; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.327) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for covariates, lovastatin use was significantly associated with increased risk of incident diabetes mellitus [OR=3.565; 99% C.I.=3.051 – 4.165; p<0.0001]. In other words, the odds of incident diabetes for lovastatin users were 3.565 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing lovastatin users to non-statin users increased marginally and remained significant [OR=3.610; 99% C.I.=3.092 – 4.215; p<0.0001]. [**Conclusion: alternative hypothesis H_{11e} was supported].**

Table 4.47: Logistic Regression Model Comparing Incident Diabetes between Lovastatin Users and Non-statin Users while Controlling for Covariates (N=62,166)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Lovastatin[a]	1.271	0.060	442.002	**p<0.0001**	**3.565**	**3.051**	**4.165**
Age	0.038	0.002	344.972	p<0.0001	1.039	1.033	1.044
Gender: Male[b]	-0.063	0.042	2.296	0.130	0.939	0.843	1.045
Hyperlipidemia	-0.178	0.068	6.971	0.008	0.837	0.703	0.996
Obesity	0.475	0.204	5.431	0.020	1.609	0.951	2.720
Hypertension	0.631	0.066	90.109	p<0.0001	1.880	1.584	2.231
Diabetogenic medications	-0.057	0.006	96.347	p<0.0001	0.944	0.930	0.959
CCI score	0.171	0.027	38.749	p<0.0001	1.187	1.106	1.274
Constant	-4.989	0.097	2,650.133	p<0.0001	0.007	-	-

Model Parameters: χ^2=1,322.8; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing lovastatin users to non-statin users increased and remained significant [OR=4.742; 99% C.I.=4.159 – 5.408; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing lovastatin users to non-statin users increased marginally and remained significant [OR=3.610; 99% C.I.=3.092 – 4.215; p<0.0001].

4.6.5 Pravastatin

H_{11f}: The proportion of pravastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Table 4.48 shows incident diabetes distribution for pravastatin users and non-statin users. An unadjusted chi-square analysis showed that the proportion of pravastatin users with incident diabetes (9.2%, N=587) was higher compared to the proportion of non-statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 537.1; df=1; p<0.0001).

Table 4.48: Frequency and Percent of Pravastatin Users and Non-statin Users with Incident Diabetes

Diabetes	Pravastatin Users N (%)	Non-statin Users N (%)	Total N (%)
Yes	587 (9.2)	1,915 (3.3)	2,502 (3.9)
No	5,796 (90.8)	56,197 (96.7)	61,993 (96.1)
Total	6,383 (100.0)	58,112 (100.0)	64,495 (100.0)

χ^2=537.1; df=1; p<0.0001

Table 4.49 shows the results of the binary logistic regression model comparing the odds of incident diabetes between pravastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,048.5; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.247) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for covariates, pravastatin use was significantly associated with increased risk of incident diabetes mellitus [OR=1.952; 99% C.I.=1.663 – 2.290; p<0.0001]. In other words, the odds of incident diabetes for pravastatin users were 1.952 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing pravastatin users to non-statin users increased marginally and remained significant [OR=1.953; 99% C.I.=1.664 – 2.292; p<0.0001]. [**Conclusion: alternative hypothesis H_{11f} was supported].**

Table 4.49: Logistic Regression Model Comparing Incident Diabetes between Pravastatin Users and Non-statin Users while Controlling for Covariates (N=64,495)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Pravastatin[a]	0.669	0.062	115.773	**p<0.0001**	**1.952**	**1.663**	**2.290**
Age	0.038	0.002	349.001	p<0.0001	1.039	1.034	1.045
Gender: Male[b]	-0.069	0.041	2.743	0.098	0.934	0.839	1.039
Hyperlipidemia	-0.143	0.063	5.174	0.023	0.866	0.737	1.019
Obesity	0.201	0.302	0.444	0.505	1.223	0.562	2.661
Hypertension	0.652	0.062	110.212	p<0.0001	1.920	1.636	2.253
Diabetogenic medications	-0.043	0.005	67.234	p<0.0001	0.958	0.945	0.971
CCI score	0.193	0.023	68.223	p<0.0001	1.213	1.142	1.289
Constant	-5.007	0.097	2,673.707	p<0.0001	0.007	-	-

Model Parameters: χ^2=1,048.5; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing pravastatin users to non-statin users increased and remained significant [OR=2.972; 99% C.I.=2.619 – 3.373; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing pravastatin users to non-statin users increased marginally and remained significant [OR=1.953; 99% C.I.=1.664 – 2.292; p<0.0001].

4.6.6 Rosuvastatin

H_{11f}: The proportion of rosuvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Table 4.50 shows incident diabetes distribution for rosuvastatin users and non-statin users. An unadjusted chi-square analysis showed that the proportion of rosuvastatin users with incident diabetes (8.1%, N=242) was higher compared to the proportion of non-statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 192.7; df=1; p<0.0001).

Table 4.50: Frequency and Percent of Rosuvastatin Users and Non-statin Users with Incident Diabetes

Diabetes	Rosuvastatin Users N (%)	Non-statin Users N (%)	Total N (%)
Yes	242 (8.1)	1,915 (3.3)	2,157 (3.5)
No	2,745 (91.9)	56,197 (96.7)	58,942 (96.5)
Total	2,987 (100.0)	58,112 (100.0)	61,099 (100.0)

χ^2=192.7; df=1; p<0.0001

Table 4.51 shows the results of the binary logistic regression model comparing the odds of incident diabetes between rosuvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=701.3; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.05) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for covariates, rosuvastatin use was significantly associated with increased risk of incident diabetes mellitus [OR=1.495; 99% C.I.=1.199 – 1.865; p<0.0001]. In other words, the odds of incident diabetes for rosuvastatin users were 1.495 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing rosuvastatin users to non-statin users increased marginally and remained significant [OR=1.500; 99% C.I.=1.203 – 1.871; p<0.0001]. [**Conclusion: alternative hypothesis H_{11g} was supported].**

Table 4.51: Logistic Regression Model Comparing Incident Diabetes between Rosuvastatin Users and Non-statin Users while Controlling for Covariates (N=61,099)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Rosuvastatin[a]	0.402	0.086	22.000	**p<0.0001**	**1.495**	**1.199**	**1.865**
Age	0.037	0.002	303.221	p<0.0001	1.038	1.032	1.043
Gender: Male[b]	-0.068	0.044	2.318	0.128	0.935	0.833	1.048
Hyperlipidemia	-0.013	0.073	0.030	0.862	0.987	0.818	1.191
Obesity	0.583	0.292	3.984	0.046	1.791	0.844	3.801
Hypertension	0.742	0.071	109.468	p<0.0001	2.099	1.749	2.520
Diabetogenic medications	-0.029	0.006	21.163	p<0.0001	0.971	0.956	0.987
CCI score	0.205	0.027	56.259	p<0.0001	1.227	1.144	1.317
Constant	-4.975	0.099	2,505.964	p<0.0001	0.007	-	-

Model Parameters: χ^2=701.3; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing rosuvastatin users to non-statin users increased and remained significant [OR=2.587; 99% C.I.=2.155 – 3.106; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing rosuvastatin users to non-statin users increased marginally and remained significant [OR=1.500; 99% C.I.=1.203 – 1.871; p<0.0001].

4.6.7 Simvastatin

H_{11f}: The proportion of simvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates.

Table 4.52 shows incident diabetes distribution for simvastatin users and non-statin users. An unadjusted chi-square analysis showed that the proportion of simvastatin users with incident diabetes (10.5%, N=1,403) was higher compared to the proportion of non-statin users with incident diabetes (3.3%, N=1,915) (χ^2 = 1,264.2; df=1; p<0.0001).

Table 4.52: Frequency and Percent of Simvastatin Users and Non-statin Users with Incident Diabetes

Diabetes	Simvastatin Users N (%)	Non-statin Users N (%)	Total N (%)
Yes	1,403 (10.5)	1,915 (3.3)	3,318 (4.6)
No	12,012 (89.5)	56,197 (96.7)	68,209 (95.4)
Total	13,415 (100.0)	58,112 (100.0)	71,527 (100.0)

χ^2=1,264.2; df=1; p<0.0001

Table 4.53 shows the results of the binary logistic regression model comparing the odds of incident diabetes between simvastatin users and non-statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,814.5; df=8, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.290) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to no statin use, and controlling for covariates, simvastatin use was significantly associated with increased risk of incident diabetes mellitus [OR=2.651; 99% C.I.=2.347 – 2.994; p<0.0001]. In other words, the odds of incident diabetes for simvastatin users were 2.651 times the odds of incident diabetes for non-statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing simvastatin users to non-statin users increased marginally and remained significant [OR=2.658; 99% C.I.=2.354 – 3.002; p<0.0001]. [**Conclusion: alternative hypothesis H_{11g} was supported].**

Table 4.53: Logistic Regression Model Comparing Incident Diabetes between Simvastatin Users and Non-statin Users while Controlling for Covariates (N=71,527)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Simvastatin[a]	0.975	0.047	426.171	**p<0.0001**	**2.651**	**2.347**	**2.994**
Age	0.037	0.002	391.723	p<0.0001	1.038	1.033	1.043
Gender: Male[b]	-0.016	0.036	0.183	0.669	0.985	0.897	1.081
Hyperlipidemia	-0.310	0.050	38.862	p<0.0001	0.733	0.645	0.834
Obesity	0.652	0.204	10.234	0.001	1.919	1.135	3.244
Hypertension	0.505	0.050	102.804	p<0.0001	1.657	1.457	1.884
Diabetogenic medications	-0.050	0.004	160.006	p<0.0001	0.951	0.942	0.961
CCI score	0.149	0.018	69.685	p<0.0001	1.161	1.109	1.215
Constant	-4.968	0.090	3042.707	p<0.0001	0.007	-	-

Model Parameters: χ^2=1,814.5; df=8, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing simvastatin users to non-statin users increased and remained significant [OR=3.428; 99% C.I.=3.120 – 3.766; p<0.0001].
Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing simvastatin users to non-statin users increased marginally and remained significant [OR=2.658; 99% C.I.=2.354 – 3.002; p<0.0001].

4.6.8 Dosage Intensity

Objective 12: To assess whether incidence of diabetes differed between intensive-dose statin users and moderate-dose statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, CCI score, and medication adherence).

H_{12}: The proportion of intensive-dose statin users with incident diabetes will be significantly higher than that of moderate-dose statin users while controlling for age, gender and clinical covariates.

Table 4.54 shows incident diabetes distribution for intensive-dose statin users and moderate-dose statin users. An unadjusted chi-square analysis showed that the proportion of intensive-dose statin users with incident diabetes (13.4%, N=831) was higher compared to the proportion of moderate-dose statin users with incident diabetes (9.3%, N=4,847) (χ^2 = 103.4; df=1; p<0.0001).

Table 4.54: Frequency and Percent of Intensive and Moderate-dose Statin Users with Incident Diabetes

Diabetes	Intensive-dose N (%)	Moderate-dose N (%)	Total N (%)
Yes	831 (13.4)	4,847 (9.3)	5,678 (9.8)
No	5,374 (86.6)	47,060 (90.7)	52,434 (90.2)
Total	6,205 (100.0)	51,907 (100.0)	58,112 (100.0)

χ^2 = 103.4; df=1; p<0.0001

Table 4.55 shows the results of the binary logistic regression model comparing the odds of incident diabetes between intensive-dose statin users and moderate-dose statin users while controlling for covariates. The overall model was statistically significant (χ^2=1,339.2; df=9, p<0.0001). This means that at least one of the predictor variables was significantly associated with the dependent variable (incident diabetes). Furthermore, the p-value (p=0.011) associated with the Hosmer-Lemeshow goodness of fit test was greater than 0.01. This shows that the logit model was a good fitting model.

Compared to moderate-dose statin use, and controlling for covariates, intensive-dose statin use was significantly associated with increased risk of incident diabetes mellitus [OR=1.578; 99% C.I.=1.414 – 1.761; p<0.0001]. In other words, the odds of incident diabetes for intensive-dose statin users were 1.578 times the odds of incident diabetes for moderate-dose statin users. However, when obesity was not controlled for in another separate model, the odds ratio comparing intensive-dose statin users to moderate-dose statin users did not change and remained significant [OR=1.578; 99% C.I.=1.414 – 1.761; p<0.0001]. [**Conclusion: alternative hypothesis H_{12} was supported].**

Table 4.56 is a summary that gives a visual comparison of the strength of association (i.e., odds ratios) between different statin use and incident diabetes.

Table 4.55: Logistic Regression Model Comparing Incident Diabetes between Intensive-dose Statin Users and Moderate-dose Statin Users while Controlling for Covariates (N=50,557)[a]							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Odds ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Dosage intensity: Intensive-dose[b]	0.456	0.043	114.477	**p<0.0001**	**1.578**	**1.414**	**1.761**
Age	0.027	0.002	160.577	p<0.0001	1.028	1.022	1.034
Gender: Male[c]	-0.112	0.031	13.455	p<0.0001	0.894	0.826	0.967
Hyperlipidemia	-0.533	0.031	300.554	p<0.0001	0.587	0.542	0.635
Obesity	0.620	0.126	24.293	p<0.0001	1.858	1.344	2.569
Hypertension	0.299	0.032	87.163	p<0.0001	1.348	1.241	1.464
Diabetogenic medications	-0.054	0.002	515.364	p<0.0001	0.947	0.942	0.953
CCI score	0.133	0.012	116.751	p<0.0001	1.142	1.107	1.179
Adherence (MPR)[d]	-0.013	0.060	0.045	0.831	0.987	0.847	1.152
Constant	-3.299	0.122	729.184	p<0.0001	0.037		

Model Parameters: χ^2=1,339.2; df=9, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]N is less than 58,112 because of missing values for MPR. MPR values was set to missing for cases with only one prescription of the statin filled (MPR numerator and denominator=0), or if two or more prescriptions filled, one or more number of days supply is 0 or negative (MPR numerator=0).

[b]Reference=Moderate-dose statin users.

[c]Reference=Female.

[d]Adherence evaluated using the medication possession ratio, MPR.

Sensitivity Analysis I: When none of the model covariates were controlled for in a separate model, the odds ratio comparing intensive-dose statin users to moderate-dose statin users decreased and remained significant [OR=1.501; 99% C.I.=1.354 – 1.665; p<0.0001].

Sensitivity Analysis II: When obesity was not controlled for in another separate model, the odds ratio comparing statin users to non-statin users did not change and remained significant [OR=1.578; 99% C.I.=1.414 – 1.761; p<0.0001].

Table 4.56: A Summary Showing the Statistical Significance of the Odds Ratios of the Association between Statin Use and Incident Diabetes (Logistic Regression)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Odds Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	1.038	0.033	993.897	p<0.0001	**2.824**	2.594	3.074
Atorvastatin[a,c]	0.910	0.039	538.842	p<0.0001	**2.485**	2.246	2.749
Fluvastatin[a,c]	0.771	0.092	69.572	p<0.0001	**2.161**	1.704	2.742
Lovastatin[a,c]	1.271	0.060	442.002	p<0.0001	**3.565**	3.051	4.165
Pravastatin[a,c]	0.669	0.062	115.773	p<0.0001	**1.952**	1.663	2.290
Rosuvastatin[a,c]	0.402	0.086	22.000	p<0.0001	**1.495**	1.199	1.865
Simvastatin[a,c]	0.975	0.047	426.171	p<0.0001	**2.651**	2.347	2.994
Intensive-dose statin[b,d]	0.456	0.043	114.477	p<0.0001	**1.578**	1.414	1.761

[Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Moderate-dose statin.

[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.

[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

4.4 SUMMARY OF HYPOTHESES TESTS

Table 4.57 presents a summary of all the hypotheses tested in the study. A total of 35 hypotheses (24 alternative and 11 null) were tested. All alternative hypotheses were supported, while all null hypotheses were rejected except null hypothesis $H_{0(5g)}$.

Table 4.57: Summary of Study Hypotheses

Study Hypothesis	Description	Conclusion: Supported/Rejected
AIM 1: TO COMPARE THE DEMOGRAPHIC (I.E., AGE AND GENDER), AND CLINICAL CHARACTERISTICS (I.E., HYPERLIPIDEMIA, OBESITY, HYPERTENSION, DIABETOGENIC MEDICATION USE, AND CCI SCORE) BETWEEN STATIN USERS AND NON-STATIN USERS **(OBJECTIVES 1 – 6)**		
Objective 1: To assess whether demographic characteristics (i.e., age and gender) differs between statin users and non-statin users		
H_{1a}	Statin users will have a significantly higher mean age compared to non-statin users	**Supported**
H_{1b}	There is a significant association between the exposure group (i.e., statin users and non-statin users) and gender	**Supported**
Objective 2: To assess whether hyperlipidemia diagnosis differs between statin users and non-statin users		
H_2	The proportion of statin users with a hyperlipidemia diagnosis will be significantly higher compared to that of non-statin users	**Supported**
Objective 3: To assess whether obesity diagnosis differs between statin users and non-statin users		
$H_{0(3)}$	There is no significant difference in the proportion of statin users and non-statin users who have an obesity diagnosis	**Rejected**

Table 4.57: Summary of Study Hypotheses (cont'd)		
Study Hypothesis	**Description**	**Conclusion: Supported/Rejected**
Objective 4: To assess whether hypertension diagnosis differs between statin users and non-statin users		
$\mathbf{H_4}$	The proportion of statin users with a hypertension diagnosis will be significantly higher compared to that of non-statin users	**Supported**
Objective 5: To assess whether the mean number of prescriptions for all diabetogenic medications differs between statin users and non-statin users		
$\mathbf{H_{0(5a)}}$	There is no significant difference in the mean number of prescriptions for all diabetogenic medications between statin users and non-statin users	**Rejected**
$\mathbf{H_{0(5b\text{-}f)}}$	There is no significant difference in the mean number of prescriptions for each diabetogenic medication (i.e., thiazide diuretics [$\mathbf{H_{0(5b)}}$], β-blockers [$\mathbf{H_{0(5c)}}$], antipsychotics [$\mathbf{H_{0(5d)}}$], antidepressants[$\mathbf{H_{0(5e)}}$], and immunosuppressants [$\mathbf{H_{0(5f)}}$] between statin users and non-statin users	**Rejected**
$\mathbf{H_{0(5g)}}$	There is no significant difference in the mean number of glucocorticoids prescriptions for statin users and non-statin users	**Supported**
Objective 6: To compare the mean CCI score between statin users and non-statin users		
$\mathbf{H_{0(6)}}$	There is no significant difference in the mean CCI score between statin users and non-statin users	**Rejected**

Table 4.57: Summary of Study Hypotheses (cont'd)		
Study Hypothesis	**Description**	**Conclusion: Supported/Rejected**
AIM 2: TO COMPARE MEDICATION ADHERENCE AMONG USERS OF EACH STATIN TYPE, AND BETWEEN INTENSIVE-DOSE STATIN USERS AND MODERATE-DOSE STATIN USERS (**OBJECTIVE 7**)		
Objective 7: To assess whether medication adherence (using MPR) differs among users of each statin type, and between intensive-dose statin users and moderate-dose statin users		
$\mathbf{H_{0(7a)}}$	There is no significant difference in mean MPR among users of each statin type	**Rejected**
$\mathbf{H_{7b}}$	Mean MPR will be significantly lower among intensive-dose statin users compared to moderate-dose statin users	**Supported**
AIM 3: USING SURVIVAL ANALYSIS, TO COMPARE TIME TO DIABETES (OR SURVIVAL TIME) BETWEEN STATIN USERS AND NON-STATIN USERS, BETWEEN USERS OF EACH STATIN TYPE AND NON-STATIN USERS, AND BETWEEN INTENSIVE-DOSE STATIN USERS AND MODERATE-DOSE STATIN USERS (**OBJECTIVES 8 – 10**).		
Objective 8 (Survival Analysis – Log-rank test and Kaplan-Meier Curves): To assess whether survival time (i.e., time to occurrence of diabetes) differs between statin users and non-statin users, among users of each statin type, and between intensive-dose statin users and moderate-dose statin users		
$\mathbf{H_{8a}}$	Statin users will have a shorter survival time compared to non-statin users	**Supported**
$\mathbf{H_{0(8b)}}$	There is no significant difference in mean survival time among users of each statin type	**Rejected**
$\mathbf{H_{8c}}$	Intensive-dose statin users will have a shorter survival time compared to moderate-dose statin users	**Supported**

Table 4.57: Summary of Study Hypotheses (cont'd)		
Study Hypothesis	**Description**	**Conclusion: Supported/Rejected**
Objective 9 (Survival Analysis – Cox Regression): To assess whether survival times differ between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score)		
H_{9a}	Statin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**
H_{9b}	Atorvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**
H_{9c}	Fluvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**
H_{9d}	Lovastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**
H_{9e}	Pravastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**

Table 4.57: Summary of Study Hypotheses (cont'd)		
Study Hypothesis	**Description**	**Conclusion: Supported/Rejected**
H_{9f}	Rosuvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**
H_{9g}	Simvastatin users will have a significantly shorter survival time compared to non-statin users while controlling for age, gender, and clinical covariates	**Supported**
Objective 10 (Survival Analysis – Cox Regression): To assess whether survival times differ between intensive-dose statin users and moderate-dose statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, CCI score, and medication adherence)		
H_{10}	Intensive-dose statin users will have a significantly shorter survival time compared to moderate-dose statin users while controlling for age, gender, and clinical covariates	**Supported**
AIM 4: USING BINARY LOGISTIC REGRESSION ANALYSIS, TO COMPARE INCIDENCE OF DIABETES BETWEEN STATIN USERS AND NON-STATIN USERS, BETWEEN USERS OF EACH STATIN TYPE AND NON-STATIN USERS, AND BETWEEN INTENSIVE-DOSE STATIN USERS AND MODERATE-DOSE STATIN USERS (**OBJECTIVES 11 & 12**)		
Objective 11 (Binary Logistic Regression): To assess whether incidence of diabetes differs between statin users and non-statin users, and between users of each statin type and non-statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score)		

Table 4.57: Summary of Study Hypotheses (cont'd)		
Study Hypothesis	**Description**	**Conclusion: Supported/Rejected**
H_{11a}	The proportion of statin users with incident diabetes will be significantly higher compared to that of non-statin users	**Supported**
H_{11b}	The proportion of statin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**
H_{11c}	The proportion of atorvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**
H_{11d}	The proportion of fluvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**
H_{11e}	The proportion of lovastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**
H_{11f}	The proportion of pravastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**
H_{11g}	The proportion of rosuvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**

Table 4.57: Summary of Study Hypotheses (cont'd)		
Study Hypothesis	**Description**	**Conclusion: Supported/Rejected**
$\mathbf{H_{11h}}$	The proportion of simvastatin users with incident diabetes will be significantly higher than that of non-statin users while controlling for age, gender and clinical covariates	**Supported**
Objective 12 (Binary Logistic Regression): To assess whether incidence of diabetes differs between intensive-dose statin users and moderate-dose statin users, while controlling for demographic variables (i.e., age and gender), and clinical covariates (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, CCI score, and medication adherence)		
$\mathbf{H_{12}}$	The proportion of intensive-dose statin users with incident diabetes will be significantly higher than that of moderate-dose statin users while controlling for age, gender and clinical covariates	**Supported**

Number of alternative hypotheses not supported=0.
Number of null hypotheses not rejected=1 [$\mathbf{H_{0(5g)}}$].

CHAPTER 5: DISCUSSION AND CONCLUSIONS

This chapter presents an in-depth discussion of the study results. First, the result of the differences in demographic and clinical characteristics between statin users and non-statin users is discussed. This is followed by a discussion of the rates of incident diabetes among the study population compared to rates found in the US population and similar studies of statin use and incidence of diabetes. The hazards and odds of diabetes that were associated with statin use as a class, with each statin type, and with different statin dosage intensities are discussed and compared with risk ratios obtained in similar observational studies of statin use and incidence of diabetes. Lastly, the study strengths, study limitations, suggestions for future research, and study implications are discussed.

5.1 REVIEW OF BACKGROUD AND STUDY PURPOSE

The FDA approved labeling changes to statins in February 2012 to include an increased risk of incident diabetes mellitus due to increases in glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG) that were found to be associated with statin therapy.[422] The decision to approve these labeling changes was based on results from RCTs,[423] meta-analyses of RCTs,[424] systematic review,[425] and a few observational

[422] Food and Drug Administration, "FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs".

[423] Thongtang N et al., "Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation."; Koh KK et al., "Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients."; Sabatine MS et al., "High-dose atorvastatin associated with worse glycemic control: a PROVE-IT TIMI 22 substudy."; Ridker PM et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein."

[424] Mills EJ et al., "Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials."; Sattar N et al., "Statins and risk of incident

studies[426] which suggest an increased risk of incident diabetes due to statin therapy. Several studies have also discussed whether the cardiovascular gain by using high dose statins may be offset by an increased risk in diabetes.[427]

The majority of previously published observational studies that had evaluated the association of statin therapy and development of new-onset diabetes used non-US population data. Because the US population may be different than other populations in terms of the prevalence of risk factors such as overweight, obesity, and cardiovascular diseases that may put people at an increased risk of diabetes that is independent of the effects of statins,[428] there is a need to further investigate this phenomenon among the US population. Thus, this need informed the two study purposes.

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diabetes: a collaborative meta-analysis of randomised statin trials."; Rajpathak SN et al., "Statin therapy and risk of developing type 2 diabetes: a meta-analysis."

[425] Kostapanos MS et al., "Do statins beneficially or adversely affect glucose homeostasis?."

[426] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."

[427] Cannon CP et al., "Intensive versus moderate lipid lowering with statins after acute coronary syndromes."; LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. Ibid.2005;352(14):1425-35; Armitage J et al., "Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial."; Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Ibid.:1670-81; de Lemos JA et al., "Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial."; ibid.; Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. Ibid.2005;294(19):2437-45; ibid.; Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."; Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

[428] Graham I et al., "Dyslipidemias in the prevention of cardiovascular disease: risks and causality."; Kirkman MS et al., "Diabetes in older adults."; Lawrence JM et al., "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005."

The first purpose of this study was to examine whether the development of incident diabetes differed between statin users (the exposed group) and non-statin users (the unexposed group), and between users of each statin type and non-statin users.

The second purpose of this study was to examine whether the development of incident diabetes differed by the intensity of the statin dosages (i.e., intensive-dose statin vs. moderate-dose statin) to which subjects were exposed. In addition to these two main study purposes, two types of statistical analyses (Cox regression and logistic regression) were conducted to examine the risk of diabetes associated with statin use. The magnitude of the risk ratios (i.e., hazard ratio and odds ratio, respectively) obtained from these two analyses were then compared for consistency.

5.2 REVIEW OF STUDY OBJECTIVES

Twelve study objectives (and 35 hypotheses) were examined in the overall aim of assessing the association between statin use and incidence of diabetes. However, these 12 objectives were reduced to four interrelated themes that focused on achieving the overall study aim.

I. Demographic and Clinical Characteristics

Objectives 1 – 6 compared the demographic (i.e., age and gender), and clinical characteristics (i.e., hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score) between statin users and non-statin users. This comparison was necessary to be sure the two groups being compared are similar on these diabetes risk factors. A statistically significant difference (or association) between the two groups on any demographic or clinical characteristic should warrant controlling for such variable(s) in all regression analyses comparing the risk of diabetes between statin users and non-statin users. Furthermore, medication adherence was compared among users of each statin type and between intensive-dose statin users and moderate-dose statin users (objective 7).

II. Statins Users vs. Non-statin Users and Incidence of Diabetes

Objective 8 (hypothesis 8a: KM curves and log-rank test) compared the survival time and the probability of survival over time for statin users and non-statin users without controlling for any confounding variable. However, objective 9 (hypothesis 9a: Cox regression) compared survival time (i.e., time from receipt of the index medication to development of incident diabetes) between statin users and non-statin users while

controlling for demographic and clinical variables. Similarly, objective 11 (hypothesis 11b: logistic regression) compared incidence of diabetes between statin users and non-statin users while controlling for demographic and clinical variables.

III. Users of Each Statin Type vs. Non-statin Users and Incidence of Diabetes

Objective 8 (hypothesis 8b: KM curves and log-rank test) compared the survival time and the probability of survival over time for users of each statin type without controlling for any confounding variable. However, objective 9 (hypotheses 9b-g: six different Cox regression models) compared survival time between users of each statin type (i.e., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) and non-statin users while controlling for demographic and clinical variables. Similarly, objective 11 (hypotheses 11c-h: six different logistic regression models) compared incidence of diabetes between users of each statin type and non-statin users while controlling for demographic and clinical variables.

IV. Intensive-dose Statin Users vs. Moderate-dose Statin Users and Incidence of Diabetes

Objective 8 (hypothesis 8c: KM curves and log-rank test) compared the survival time and the probability of survival over time for intensive-dose and moderate-dose statin users without controlling for any confounding variable. However, objective 10 (hypothesis 10: Cox regression) compared survival time between intensive-dose statin users and moderate-dose statin users while controlling for medication adherence, and demographic and clinical variables. Similarly, objective 12 (hypothesis 12: logistic

regression) compared incidence of diabetes between intensive-dose statin users and moderate-dose statin users while controlling for medication adherence, and demographic and clinical variables.

5.3 DEMOGRAPHIC CHARACTERISTICS AND CLINICAL COVARIATES

A total of 13 hypotheses (4 alternative and 9 null) were tested by univariate analyses (i.e., t-tests and chi-square tests) to assess if statin users differed significantly from non-statin users on important demographic characteristics such as age and gender, and on clinical characteristics such as hyperlipidemia, obesity, hypertension, diabetogenic medication use, and CCI score. If the two groups differed significantly on any of these variables (and because these variables are important risk factors for diabetes), then it is important that such variable(s) be controlled for in all regression models that examined the association between statin use and incident diabetes.

A discussion of the differences in demographic and clinical variables between statin users and non-statin users that were examined by univariate analyses is presented below.

5.3.1 Age

Age is an independent risk factor for diabetes mellitus because diabetes risk increases as age increases.[429] Results of the univariate t-test indicated that mean age (in years) was significantly higher ($p<0.0001$) among statin users (52.2) compared to non-statin users (40.6). This result is in line with what was hypothesized and was expected because the prevalence of high LDL-C (defined as level that is at or above LDL-C goal for a patient's cardiovascular risk group, or current use of cholesterol medication) among

[429] American Diabetes Association. Standards of medical care in diabetes--2014. Ibid.2014;37 Suppl 1:S14-80.

Americans increases with age.[430] This means that statin users are older than the average American population.

This result is consistent with results of similar observational studies of statin use and incidence of diabetes. The mean age of statin users or statin initiators (64.1) was higher than that of non-statin users or non-initiators (61.3) in the Danaei et al. study.[431] This UK-based study examined the risk of diabetes among 285,864 men and women who were aged 50 – 84 years. Similarly, the mean age of statin users was higher than those of non-statin users, respectively, in the Sukhija et al. (69 vs. 63; $p<0.0001$),[432] Culver et al. (65.7 vs. 62.9; $p<0.001$),[433] and Izzo et al. (62.5 vs. 57.9; $p<0.0001$)[434] observational studies of statin use and incidence of diabetes.

In addition, when age was categorized into four age groups (i.e., 20 – 34, 35 – 44, 45 – 54, and 55 – 63 years), there was a significant association ($p<0.0001$) between whether a subject took statin medication or not and the different age categories. Specifically, the majority of statin users (83.6%) were aged 45 years or older whereas the majority of non-statin users (59.6%) were below 45 years of age. This finding is reasonable because, in addition to LDL-C values, age ≥45 years in men or ≥55 years in women is a major risk factor for dyslipidemia and atherosclerotic cardiovascular disease

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430 Centers for Disease Control and Prevention, "Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008."
431 Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
432 Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
433 Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."
434 Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

(ASCVD) – the two main indications for statin use.[435] Furthermore, prevalence of high LDL-C (thus, statin use) was correlated with age. Among Americans aged 20 years or older, the prevalence of high LDL-C was highest among those 65 years or older (58.2%) compared to those aged 40 – 64 years (41.2%) and 20 – 39 years (11.7%).[436]

[435] "Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)."
[436] Centers for Disease Control and Prevention, "Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008."

5.3.2 Gender

Among US adult population aged 20 years or older, the prevalence of diabetes differs by gender. Diabetes prevalence is higher among males (13.6%) compared to females (11.2%).[437] This study's results showed there was a gender difference between statin users and non-statin users. Because the need for cardiovascular protection and use of statins are associated more with males,[438] we expected the majority of statin users to be males. The study results barely supported this hypothesis as the proportion of statin users that were males (50.2%) was almost equal to the proportion of statin users that were females (49.8%). The association of the male gender with statin use is consistent with previous research. A study that examined the prevalence of high LDL-C among American adults who were aged 20 years and older found that the proportion of males with high LDL-C (36.2%) was higher compared to the proportion of females with high LDL-C (31%).[439]

This observation is also consistent with previous research of statin use and incidence of diabetes. Izzo et al. reported a higher proportion of males among statin users (51%) compared to the proportion of females among statin users (49%).[440] Similarly, the proportion of males among statin users was higher than the proportion of females among

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[437] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."
[438] Cho L, Hoogwerf B, Huang J, Brennan DM, and Hazen SL. Gender differences in utilization of effective cardiovascular secondary prevention: A cleveland clinic prevention database study. J Womens Health. 2008;17(4):515-21.
[439] Centers for Disease Control and Prevention, "Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008."
[440] Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

statin users, respectively, in the Danaei et al. (50.2% vs. 49.8%),[441] Ko et al. (53.7% vs. 46.3%),[442] and Sukhija et al. (98% vs. 2%)[443]studies. The Sukhija et al. study was a retrospective cohort study which examined the effects of statin therapy on fasting plasma glucose among 345,417 United States military veterans.[444] However, the gender direction for non-statin users was unclear because there is more theoretical interest in statin use than non-use.

[441] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[442] Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."
[443] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
[444] Ibid.

5.3.3 Hyperlipidemia

Hyperlipidemia is a risk factor for metabolic syndrome and cardiovascular diseases,[445] which are in turn risk factors for diabetes mellitus.[446] Among the study population, 28% had a diagnosis of hyperlipidemia. This hyperlipidemia prevalence among the study population was consistent but lower compared to the proportion of American adults aged 20 years and older with high LDL-C (34%).[447] Because the prevalence of hyperlipidemia has been shown to increase with age, the lower prevalence of hyperlipidemia as found in this study might be due to the lower age range (20 – 63 years) of the study population. One study showed that the prevalence of high LDL-C among Americans is highest among those aged 65 years or older (58.2%) compared to those aged 40 – 64 years (41.2%) or 20 – 39 years (11.7%).[448]

Furthermore, the result of a chi-square analysis showed that the proportion of statin users with a diagnosis of hyperlipidemia (49.8%) was higher compared to the proportion of non-statin users with a diagnosis of hyperlipidemia (6.1%). This result is in line with what was hypothesized and was expected because statins are indicated for the management of hyperlipidemia and cardiovascular disease. Statins are used for most forms of dyslipidemias, including hypercholesterolemia (high TC) and

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[445] Wilson PW et al., "Prediction of coronary heart disease using risk factor categories."; "The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease."; "Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering."
[446] Carr MC and Brunzell JD, "Abdominal obesity and dyslipidemia in the metabolic syndrome: Importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk."
[447] Centers for Disease Control and Prevention, "Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008."
[448] Ibid.

hypertriglyceridemia (high TG). In addition, statin therapies are also used to either prevent the incidence of CHD through reduction of the risk factors associated with CHD (i.e., primary prevention), or they are used in secondary prevention to reduce the incidence and prevalence of recurrent CHD in people with established CHD.[449]

The result of this study is consistent with those of previous observational studies of statin use and incidence of diabetes that compared mean cholesterol (i.e., TC and LDL-C) levels among statin users and non-statin users.[450] Mean LDL cholesterol (in mg/dL) was higher among statin users compared to non-statin users, respectively, in the Danaei et al. (161.6 vs. 134.6)[451] and Sukhija et al. (116 vs. 111; $p<0.0001$)[452] studies. In addition, Izzo et al. reported that mean total cholesterol and non-HDL cholesterol levels (in mg/dL), respectively, were significantly higher ($p<0.0001$) among statin users (217.9 and 167.2) compared to non-statin users (205.3 and 155.2).[453]

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449 "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report."
450 Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."
451 Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
452 Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
453 Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."

5.3.4 Obesity

The epidemic of gestational and type 2 diabetes in the US has been attributed to increasing rates of overweight and obesity.[454] Because obesity increases insulin resistance, overweight and obese individuals have a greater risk for diabetes.[455]

Among the study population, 0.6% had a diagnosis of obesity. This low prevalence of obesity among the study population is not consistent with the proportion of American adults aged 20 years and older who are obese (34.9%).[456] This discrepancy may be due to underreporting (or under-coding) of obesity diagnosis in administrative databases (via ICD-9-CM diagnosis codes) compared to obesity rates captured in registries (via recorded height and weight, and calculated BMIs).[457] One study reported that obesity prevalence (2.4%) was lower in an administrative database that utilized ICD-9-CM obesity codes compared to when the obesity prevalence (20.3%) for the same set of patients was estimated using a linkable registry that utilizes BMI values.[458] The disproportionate low number of patients with an obesity diagnosis code in the study sample is a limitation of this study.

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[454] Kirkman MS et al., "Diabetes in older adults."; Lawrence JM et al., "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005."
[455] Norris SL et al., "Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review."
[456] Ogden CL, Carroll MD, Kit BK, and Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311(8):806-14.
[457] Martin B-J, Chen G, Graham M, and Quan H. Coding of obesity in administrative hospital discharge abstract data: accuracy and impact for future research studies. BMC Health Serv Res. 2014;14(1):70.
[458] Ibid.

However, even though the prevalence of obesity was lower among the study population compared to the US adult population, it should be noted that the current study population is unique by itself and the result of a chi-square analysis showed that the proportion of statin users with an obesity diagnosis (1.0%) was significantly higher ($p<0.0001$) compared to the proportion of non-statin users with an obesity diagnosis (0.3%). For this reason, the obesity variable was retained as a covariate that was controlled for in all regression analyses. However, sensitivity analyses of all study results were carried out without controlling for the obesity variable. Results of the sensitivity analyses indicate that the risk ratios associating statin use with incident diabetes only increased marginally when the obesity variable was not accounted for in all regression analyses.

Moreover, the result of this study is consistent with the results of previous research that compared the extent of overweight among study populations that used or did not use statins. Danaei et al. found that mean BMI (in kg/m^2) among statin users (28.1) was higher compared to that among non-statin users (27.7).[459] Similarly, mean BMI was significantly higher ($p<0.001$) among statin users (28.56) compared to non-statin users (27.70) in the Culver et al. study of statin use and incident diabetes among postmenopausal women participating in the longitudinal Women's Health Initiative study.[460] These higher rates of overweight (defined as BMI ≥25, and by inference,

[459] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[460] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

obesity) that were observed among statin users compared to non-statin users are consistent with literature findings. This is because there is a direct relationship between hyperlipidemia, overweight/obesity, and cardiovascular diseases,[461] with overweight/obesity being a risk factor for hyperlipidemia and coronary heart disease, and hyperlipidemia and coronary heart disease being indications for statin use.

[461] "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report."

5.3.5 Hypertension

Hypertension (high blood pressure) is an independent risk factor for diabetes mellitus.[462] Among the study population, 17.5% had a hypertension diagnosis. This prevalence of hypertension recorded for the study population is comparable but lower than the 2011 – 2012 overall prevalence of hypertension (29.1%) among US adults aged 18 years and older.[463] It unknown as to why this discrepancy was found, except to say that the study population were actively employed and composed of a lower age range (20 – 63 years), whereas the US population may include non-employed and older people.

In addition, the result of a chi-square analysis showed that the proportion of statin users with a hypertension diagnosis (30.8%) was higher compared to the proportion of non-statin users with a hypertension diagnosis (4.2%). This result is in line with what was hypothesized and was expected because hypertension is a risk factor for CHD,[464] and high risk of CHD or established CHD are indications for statin use.

The study result is consistent with previous observational studies of statin use and incidence of diabetes where prevalence of hypertension among statin users and non-statin users was reported. The proportion of statin users with hypertension was higher compared to the proportion of non-statin users with hypertension, respectively, in the

462 American Diabetes Association, "Standards of medical care in diabetes--2014."
463 Nwankwo T, Yoon SS, Burt V, and Q G. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011–2012. Hyattsville, MD: National Center for Health Statistics; 2013.
464 Centers for Disease Control and Prevention, "Million Hearts: strategies to reduce the prevalence of leading cardiovascular disease risk factors in United States."

Danaei et al. (62.1% vs. 50.7%)[465] and Sukhija et al. (88% vs. 66%; p<0.0001)[466] studies. In addition, Izzo et al. reported that the mean duration of hypertension (in years) was significantly higher among statin users (7.20) compared to non-statin users (5.44).[467]

Even though the results of this study was similar to other studies in terms of the proportion of statin users with hypertension being higher than that of non-statin users with hypertension; overall, the percentages were lower in this study. This might be attributed to the fact that study participants were older in these previous studies. Among Americans aged 18 years and older, the prevalence of hypertension has been shown to be higher among those aged 60 years and above (65%) compared to those aged 40 – 59 (32.4%) and 18 – 39 (7.3%).[468] Compared to the mean age for our study population (46.4 years), the study population mean age was higher in the Sukhija et al. (61 years) and Izzo et al. (59 years) studies. The study population in the Danaei et al. study was also older, with age ranging from 50 – 84 years.

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[465] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[466] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
[467] Izzo R et al., "Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk."
[468] Nwankwo T, Yoon SS, Burt V, and Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. NCHS Data Brief. 2013(133):1-8.

5.3.6 Diabetogenic Medication Use

Certain drugs and agents have the ability to increase the risk of diabetes independent of the use of statins. These agents include thiazide diuretics,[469] β-blockers,[470] antipsychotic agents,[471] antidepressants,[472] glucocorticoids (especially prednisolone and dexamethasone),[473] and immunosuppressive agents (especially tacrolimus and cyclosporine).[474]

Study results showed that the mean number of prescriptions for all diabetogenic medications was significantly higher ($p<0.0001$) among statin users (5.7) compared to non-statin users (0.8). In addition, the proportion of statin users with at least one diabetogenic medication prescription (44.7%) was higher compared to the proportion of non-statin users with at least one diabetogenic medication prescription (12.3%). This means that statin users were at a higher risk of having diabetes, independent of their use of statins, compared to non-statin users.

When the analysis was broken down by the type of diabetogenic medications involved, the study results indicated that the proportion of statin users that received at

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469 Zillich AJ et al., "Thiazide diuretics, potassium, and the development of diabetes: A quantitative review."; Elliott WJ and Meyer PM, "Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis."

470 Kuti EL et al., "The development of new-onset type 2 diabetes associated with choosing a calcium channel blocker compared to a diuretic or beta-blocker."; Bangalore S et al., "A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus."

471 Holt RI and Peveler RC, "Association between antipsychotic drugs and diabetes."

472 Khoza S et al., "Use of antidepressants and the risk of type 2 diabetes mellitus: a nested case-control study."

473 Kwon S and Hermayer KL, "Glucocorticoid-induced hyperglycemia."

474 Penfornis A and Kury-Paulin S, "Immunosuppressive drug-induced diabetes."; Vincenti F et al., "Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus."

least one diabetogenic medication prescription was higher compared to the proportion of non-statin users that received at least one diabetogenic medication prescription, respectively, for thiazide diuretics (8.7% vs. 1.9%), beta-blockers (21.8% vs. 3.1%), antipsychotics (1.4% vs. 0.4%), antidepressants (24.6% vs. 8.3%), and immunosuppressants (0.40% vs. 0.06%). However, the proportion of statin users (0.10%) and non-statin users (0.06%) that received at least one glucocorticoid prescription was similar.

Even though there is limited information regarding the use of diabetogenic drugs among statin users; the results were consistent with the results of previous observational studies.[475] For example, the proportion of statin users who used β-blockers was higher than the proportion of non-statin users who used β-blockers, respectively, in the Danaei et al. (22.8% vs. 14.8%)[476] and Sukhija et al. (58% vs. 25%; $p<0.0001$)[477] studies. In the current study, a higher proportion of statin users used both thiazide diuretics and β-blockers compared to non-statin users. This is not unexpected because both drugs are used in the management of hypertension; and as mentioned earlier, hypertension is a risk factor for CHD,[478] and statins are indicated for prevention or management of CHD. In concordance with this observation, this study's results mentioned that the proportion of

[475] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
[476] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[477] Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."
[478] Centers for Disease Control and Prevention, "Million Hearts: strategies to reduce the prevalence of leading cardiovascular disease risk factors in United States."

statin users with a hypertension diagnosis (30.8%) was higher compared to the proportion of non-statin users with a hypertension diagnosis (4.2%). Even though the results were similar to the results obtained in the Sukhija et al. study with regards to the proportion of statin users that received at least one beta-blocker being higher compared to that of non-statin users, it is worth noting that the magnitudes of the proportions were lower in this study. This might be due to demographic differences between this study and the Sukhija et al. study. Participants in the Sukhija et al. study were predominantly males and older. Beta-blockers are used in the management of hypertension, and the prevalence of hypertension is higher among males and older people.[479]

Apart from these aforementioned antihypertensive diabetogenic medications, other diabetogenic medications mentioned in the literature included use of oral steroids and antidepressants. Our result is consistent with results of similar studies that compared the proportion of statin users and non-statin users that used antidepressants, but the result was inconsistent with previous research regarding the proportion of statin users and non-statin users who used steroids. The Danaei et al. study showed that the proportions of subjects who used oral steroids and antidepressants, respectively, were higher among statin users (2% and 9.6%) compared to non-statin users (1.8% and 8.4%).[480] Compared to our study, there is a more noticeable difference in the proportion of statin users and non-statin users that used antidepressants (24.6% vs. 8.3%). However, our study did not

[479] Nwankwo T et al., "Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012."
[480] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."

find a significant difference in the proportion of statin users and non-statin users that used glucocorticoids (0.10% vs. 0.06%).

The reasons why statin users may be more inclined to use antidepressants than the general population is unknown. However, previous research has associated increasing age and the female gender with antidepressants use among Americans aged 12 years and older.[481] In this study conducted by the CDC's National Center for Health Statistics, and using data from the 2005 – 2008 National Health and Nutrition Examination Surveys, the proportions of Americans that used antidepressants were higher among those aged 40 – 59 (15.9%) and 60+ (14.5%) compared to those aged 12 – 17 (3.7%) and 18 – 39 (6.1%). In addition, females were 2.5 times more likely to take antidepressants compared to males. The age argument is consistent with the demographics of our study population where the majority of statin users (83.6%) was aged 45 years and above, whereas the majority of non-statin users (59.6%) was aged below 45 years. Unlike the CDC study above, the gender distribution in our study cannot explain the strong association of the female gender and use of antidepressants as noted in the CDC study since statin users were composed of an almost equal proportion of females (49.8%) and males (50.2%).

[481] Pratt L, Brody D, and Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. Hyattsville, MD: National Center for Health Statistics; 2011. NCHS data brief, no 76.

5.3.7 Charlson Comorbidity Index Score

Comorbidity is the co-occurrence of two or more disease conditions in a patient. The higher the CCI score for a patient, the higher the risk of mortality associated with such two or more comorbid conditions in the patient.[482] Higher CCI scores are also predictive of complications resulting from chronic diseases such as diabetes.[483]

The study results found that the mean CCI score was significantly higher ($p<0.0001$) among statin users (0.25) compared to non-statin users (0.04). In addition, the proportion of statin users with CCI score of one or more (12.9%) was higher compared to the proportion of non-statin users with CCI score of one or more (2.3%). This finding is not surprising because it was mentioned earlier that the proportions of statin users with chronic diseases such as hyperlipidemia, obesity, and hypertension were significantly higher compared to the proportions of non-statin users with such chronic diseases. Higher CCI scores, and thus, higher likelihood of diabetes may be present among statin users compared to non-statin users because hyperlipidemia, obesity, and hypertension are common comorbid conditions in people with diabetes.[484]

Not many studies that evaluated the association between statin use and incidence of diabetes controlled for differences in CCI score between statin users and non-statin users. Nevertheless, the result of this study is consistent with the results of Danaei et al. study which compared the prevalence of certain disease conditions (used in estimating

[482] Charlson ME et al., "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation."
[483] Huang Y-q, Gou R, Diao Y-s, et al. Charlson comorbidity index helps predict the risk of mortality for patients with type 2 diabetic nephropathy. Journal of Zhejiang University. Science. B. 2014;15(1):58-66.
[484] American Diabetes Association, "Standards of medical care in diabetes--2014."

the CCI score) among statin users and non-statin users. The Danaei et al. study found that the proportions of statin users who were diagnosed with chronic pulmonary disease (4.7% vs. 3.4%), atrial fibrillation (2.2% vs. 1.6%), and rheumatoid arthritis (2.2% vs. 2%) were higher compared to the proportions of non-statin users who were diagnosed with such diseases, respectively.[485]

[485] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."

5.3.8 Statin Use and Medication Adherence

A secondary study objective was to compare medication adherence among users of each statin type and between intensive-dose statin users and moderate-dose statin users. The medication possession ratio (MPR) was used as a proxy to measure adherence to statin medications. Subjects with MPRs ≥ 80% were considered 'adherent' while those with MPRs <80% were classified as 'non-adherent.'

There is a direct correlation between statin adherence and statin efficacy. One study found that each 25% increase in adherence was associated with a ~3.8mg/dL decrease in LDL cholesterol.[486] Statin non-adherence has also been found to be associated with increased risk of mortality. One study found that the risk of mortality increased by 12 – 25% among patients with acute myocardial infarction who were non-adherent with their statin medications.[487]

In this study, the results indicated that statin users had a mean MPR of 75%, and the majority (54.2%) were adherent (i.e., had MPRs of 80 percent or higher). The rate of statin adherence in this study is comparable to that of a study similar to ours with respect to the demographics of the study population and follow-up time. In this study conducted by Pittman et al., statin users aged 18 – 61 years had a mean MPR of 82.7%, and the majority (67.6%) were adherent (i.e., MPR≥80%) after 18 months of follow-up.[488]

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[486] Ho PM, Bryson CL, and Rumsfeld JS. Medication Adherence: Its Importance in Cardiovascular Outcomes. Circulation. 2009;119(23):3028-35.
[487] Rasmussen JN, Chong A, and Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007;297(2):177-86.
[488] Pittman DG, Chen W, Bowlin SJ, and Foody JM. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. Am J Cardiol. 2011;107(11):1662-66.

However, studies have shown that statin adherence decreases with time. The rates of statin adherence might have been high in this study because of the shorter follow-up period (18 months). Subjects that are followed for a shorter period of time have fewer opportunities to discontinue their medications compared to subjects that are followed for a much longer period of time.[489] For example, several studies have reported a decreasing trend in adherence rates as the time of follow-up increases. Caspard et al. reported that 80% of statin users were adherent when followed for six months.[490] However, the proportion of statin users who were adherent with their statin medication decreases as follow-up time increases to one year (74%), two years (65%), and three years (61%). Similarly, Benner et al. reported that 79% of statin users were adherent after just three months of follow-up. However, this proportion decreased to 42% after the cohort was followed for 10 years.[491]

Predictors of Statin Non-Adherence

The results of this study indicate that medication adherence was highest among lovastatin users whereas it was lowest among fluvastatin users. Similarly, adherence was higher among moderate-dose statin users compared to intensive-dose statin users. Several factors could be responsible for differences in statin adherence from one patient to the other, or from the use of one statin type or dose to another. Since this was not the main

[489] Johnson ES, and Mozaffari E. Measuring patient persistency with drug therapy using methods for the design and analysis of natural history studies. Am J Manag Care. 2002;8(10 Suppl):S249-54.
[490] Caspard H, Chan AK, and Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. Clin Ther. 2005;27(10):1639-46.
[491] Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, and Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA. 2002;288(4):455-61.

focus of this study, such factors were not explored. However, the literature provides guidance on numerous interrelated factors that could influence adherence among statin users. These factors include patient factors such as demographics, socioeconomic status, comorbidities, and level of sensitivity of the patient to the drug's adverse effect; physician factors such as physician's demographic characteristics and interaction with patients; and health system factors such as patient cost and access to care.[492]

Patient and Physician Factors

Similar to adherence with medications in general, adherence to statins is strongly predicted by patients' demographic characteristics. A meta-analysis of 22 cohort studies in which each of the component studies evaluated adherence among statin users indicated that age, gender, and race/ethnicity were strong predictors of adherence. The meta-analysis by Mann et al. found that the association between age and adherence is not linear but is presented as an inverted 'U-shaped' relationship.[493] Younger (age <50 years) and older (age ≥70 years) adults are more likely to have lower adherence and higher discontinuation rates compared to 'middle aged' (ages 50 – 65 years) adults. The reason for this may be that younger individuals may be less likely to perceive themselves as being particularly at risk for heart diseases, whereas older individuals may have more comorbidities, more poly-pharmacy, or are more susceptible to statin adverse effects due to leaner muscle mass.

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[492] Mauskop A, and Borden WB. Predictors of statin adherence. Curr Cardiol Rep. 2011;13(6):553-8.
[493] Mann DM, Woodard M, Muntner P, Falzon L, and Kronish I. Predictors of non-adherence to statins: A systematic review and meta-analysis. Ann Pharmacother. 2010;44(9):1410-21.

In addition, the meta-analysis showed that women are generally more likely than men to have lower medication adherence.[494] One study showed that females were 11% less likely than men to be adherent with their medication.[495] Furthermore, the literature reported that minority populations may be less adherent with their medications. In one study involving a large cohort of diabetic patients, African Americans, Hispanics, and Asians were significantly less likely to be adherent with their medications compared to non-Hispanic whites.[496] However, race concordance was seen to modify the relationship between race and adherence rates, especially among African Americans. It was observed that adherence subsequently increased if both patient and physician were of the same African American race. On the other hand, medication adherence improved among Hispanic patients if there was Spanish language concordance between patients and their physicians.[497]

Apart from demographic factors, patient's socioeconomic status is also a significant determinant of medication adherence. The meta-analysis by Mann et al. showed that patients with higher income were more likely to be adherent than those with poorer income.[498] One study also showed that statin adherence was higher among patients

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494 Ibid.

495 Chan DC, Shrank WH, Cutler D, et al. Patient, physician, and payment predictors of statin adherence. Med Care. 2010;48(3):196-202.

496 Traylor AH, Schmittdiel JA, Uratsu CS, Mangione CM, and Subramanian U. Adherence to cardiovascular disease medications: does patient-provider race/ethnicity and language concordance matter? J Gen Intern Med. 2010;25(11):1172-7.

497 Ibid.

498 Mann DM et al., "Predictors of non-adherence to statins: A systematic review and meta-analysis."

living in higher income neighborhoods.[499] People with higher income may be more likely to be able to afford the cost of their medications or have better access to their physicians or may have higher education levels.

In addition to socio-economic factors and demographics characteristics, a patient's comorbidity may also be influential in long-term adherence. Research suggests that adherence is better in patients with more cardiovascular risk factors. The meta-analysis by Mann et al. showed that people with a history of myocardial infarction or stroke were 32% more likely to be adherent than those without such history.[500] Thus, statin adherence might be better among those taking statins for secondary prevention (i.e., those with established CVD) than among those using statins as primary prevention. Perhaps, the former are more motivated to take their medications due to the gravity of their condition, while the latter are not currently experiencing any adverse cardiovascular events and may sometimes question the wisdom of refilling or taking their medications.

Lastly, statin adherence may be influenced by a patients' intolerance to side effects. Even though statins are generally well tolerated and are believed to have minimal adverse effects,[501] statin therapies may be associated with bothersome side effects that are mostly related to muscle toxicity. These muscle-related problems range from muscle aches and weaknesses found in myopathies, myalgia, and myositis, to the more life-threatening condition of rhabdomyolysis (the basis on which cerivastatin was withdrawn

[499] Chan DC et al., "Patient, physician, and payment predictors of statin adherence."
[500] Mann DM et al., "Predictors of non-adherence to statins: A systematic review and meta-analysis."
[501] Pasternak RC et al., "ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins."

from the US market in 2001). One study that evaluated statin-related side effects found that 19.8% of patients with muscle-related discomfort discontinued their medications and 16.7% required a reduction in the statin dose after 3 months of initiation of statin therapy. Furthermore, most of the side effects were thought to be related to the more potent statins such as atorvastatin.[502]

The argument for a linear relationship between higher statin potency and higher discontinuation rates or low statin adherence due to adverse effects does not seem to be supported among individual statins in this study. This is because adherence was higher among users of more potent statins such as rosuvastatin (MPR=76.5) and atorvastatin (MPR=74.8) compared to users of less potent statins such as fluvastatin (MPR=72.8) and pravastatin (MPR=74.5). However, it is doubtful if the statistical significance of these marginal differences in adherence translates into practical clinical significance.

As mentioned earlier, one study indicated that there is a correlation between statin efficacy and statin adherence.[503] Thus, higher efficacy (in terms of the percent of LDL-C reductions achieved), rather than more side effect, might be the better explanation of why there was higher adherence among rosuvastatin and atorvastatin users compared to users of less efficacious statins such as fluvastatin and pravastatin. Patients may be more inclined to use their medication if they found them effective. However, the relationship between potency and adverse effect was stronger when statin dosages were accounted

[502] Bruckert E et al., "Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study."
[503] Ho PM et al., "Medication Adherence: Its Importance in Cardiovascular Outcomes."

for. As a result, intensive-dose (high potency + high dose, MPR=70.7) statin use was associated with lower adherence than moderate-dose (mainly low potency + low dose, MPR=75.6) statin use. Thus, adherence may have been lower among intensive-dose statin users compared to moderate-dose statin users due to more incidences of adverse effects.

Health Care System Factors

In addition to patient and physician factors, health care factors such as medication cost and access to care has influenced medication adherence.[504] Research has shown that medication adherence is inversely related to patient costs across many different types of drug products. The use of statin drug products follows similar patterns. For example, several studies have shown that lower copayments are associated with higher levels of statin adherence. A study by Gibson et al. shows that when copayment for a statin drug increase by $10, the likelihood of adherence was reduced by 1.8% for new statin users and by 3% for continuing statin users.[505] Another study showed that patients were 58% less likely to be adherent with their statin medications when copayment was greater than $20 compared to when copayment was $10.[506] Furthermore, a study which examined the association between out-of-pocket cost and statin utilization among Medicare Part D patients noted that the proportion of the patients who were adherent with their

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[504] Mauskop A and Borden WB, "Predictors of statin adherence."
[505] Gibson TB, Mark TL, Axelsen K, Baser O, Rublee DA, and McGuigan KA. Impact of statin copayments on adherence and medical care utilization and expenditures. Am J Manag Care. 2006;12 Spec no.:SP11-9.
[506] Ye X, Gross CR, Schommer J, Cline R, and St Peter WL. Association between copayment and adherence to statin treatment initiated after coronary heart disease hospitalization: a longitudinal, retrospective, cohort study. Clin Ther. 2007;29(12):2748-57.

medications reduced from 67% to 56%, respectively, when annual out-of-pocket costs increased from $200 to $240.[507]

In regard to access to health care, a meta-analysis by Mann et al. showed that there was no clear relationship between access to healthcare (e.g., number of healthcare provider visits) and medication adherence.[508] An increased number of physician visits was associated with better adherence in some studies,[509] while a higher number of physician visits was not associated with better adherence in other studies.[510]

[507] Karaca-Mandic P, Swenson T, Abraham JM, and Kane RL. Association of Medicare Part D medication out-of-pocket costs with utilization of statin medications. Health Serv Res. 2013;48(4):1311-33.
[508] Mann DM et al., "Predictors of non-adherence to statins: A systematic review and meta-analysis."
[509] Chodick G, Shalev V, Gerber Y, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clin Ther. 2008;30(11):2167-79; Yang CC, Jick SS, and Testa MA. Discontinuation and switching of therapy after initiation of lipid-lowering drugs: the effects of comorbidities and patient characteristics. Br J Clin Pharmacol. 2003;56(1):84-91.
[510] Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, and Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. J Gen Intern Med. 2004;19(6):638-45; Perreault S, Blais L, Lamarre D, et al. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol. 2005;59(5):564-73.

5.4 INCIDENCE OF DIABETES

The unadjusted cumulative incidence of diabetes (over 2003 – 2004) among this study population aged 20 – 63 years was 65.3 per 1,000 population (or 6.53%). This means that if 1,000 study subjects were followed from 2003 – 2004, 65.3 new cases of diabetes will be recorded. This rate is higher compared to the unadjusted incidence of diabetes of 7.8 per 1,000 population of US adults aged 20 years and over (diabetes incidence was estimated using the 2010 – 2012 National Health Interview Survey data).[511] In addition, the unadjusted cumulative incidence of diabetes among statin users and non-statin users were 98 per 1,000 population (9.8%) and 33 per 1,000 population (3.3%), respectively.

The higher rates of incident diabetes found among the study population may be attributed to the way 'new' cases of diabetes was defined in the current study. Due to the fact that study data were limited to two years in length, six months of pre-index period was used in identifying and excluding prevalent cases of diabetes. This means that only six months was used to establish a history of diabetes. The length of this pre-index period may not be sufficient. A longer data period could have allowed the flexibility to assign a longer pre-index period to identify and exclude more prevalent diabetes cases. Thus, it is possible that diabetes cases that were identified as incident cases in the current study might have been correctly classified as prevalent cases and thus excluded from the

[511] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."

numerator that was used in estimating the cumulative incidence, therefore yielding a lower value.

In addition, because statin users constituted half the study population at risk (and statin users may be more likely than the average population to have several risk factors for diabetes), it might be reasonable that the rate of incident diabetes for the current study population would be higher than that of the US population that does not have half its population at risk composed essentially of statin users.

Primarily for the first reason given above (i.e., insufficiently long observation period), the unadjusted incident density rate of diabetes obtained among this study population (4.45 per 1,000 person-months) might have been higher compared to rates obtained in similar population-based observational studies of statin use and incidence of diabetes. The unadjusted study population incident density rates of diabetes were lower in the Culver et al. (0.85 per 1,000 person-months),[512] Danaei et al. (0.96 per 1,000 person-months),[513] and Wang et al. (1.75 per 1,000 person-months)[514] studies. The observation period in this study (2003 – 2004) was shorter compared to the observation periods in the Culver et al. (1993 – 2005),[515] Danaei et al. (2000 – 2010),[516] and Wang et al. (2000 –

512 Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."
513 Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
514 Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."
515 Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."
516 Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."

2003)[517] studies. Due to the luxury of having longer observational data periods, these studies were able to assign longer pre-index periods to identify and exclude more prevalent diabetes cases.

Furthermore, only one observational study has compared diabetes incident density rates between statin users and non-statin users. The unadjusted incident density rate of diabetes reported among statin users in this study (6.82 per 1,000 person-months) was higher compared to that reported in the Danaei et al. study (1.30 per 1,000 person-months). Similarly, a higher incident density rate of diabetes was reported among non-statin users in this study (2.20 per 1,000 person-months) compared to that reported in the Danaei et al. study (0.94 per 1,000 person-months). For the same reasons given above, higher diabetes incidence density rates were reported among statin users and non-statin users in this study compared to reported rates in the literature.

Sensitivity Analysis

A sensitivity analysis was conducted to examine how varying lengths of the pre-index period affected the reclassification of incident diabetes cases as prevalent ones. Study results found in Appendix G shows that 1,777 incident diabetes cases were reclassified as prevalent diabetes cases and removed from the study cohort when the pre-index period for identifying prevalent diabetes cases was increased from six months to one year. In contrast, 5,017 incident diabetes cases were reclassified as prevalent diabetes cases and removed from the study cohort when the pre-index period for identifying

[517] Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."

prevalent diabetes cases was increased from six months to 1.5 years. In addition, the unadjusted diabetes cumulative incidence and incidence density rates decreased 'substantially' when the pre-index period was increased from six months to one year and then to 1.5 years.

5.5 STATIN USE AND INCIDENCE OF DIABETES

The main objective of this study was to investigate if statin users were at an increased risk of new-onset diabetes compared to non-statin users. Results from both the Cox regression and the logistic regression analyses indicate that statin therapy was significantly associated with increased risk of incident diabetes. The Cox regression analysis showed that the hazard of incident diabetes among statin users was 2.752 times the hazard of incident diabetes among non-statin users (HR=2.752, 99% C.I.=2.535 – 2.987). The logistic regression analysis also showed that the odds of incident diabetes among statin users was 2.824 times the odds of incident diabetes among non-statin users (OR=2.824, 99% C.I.=2.594 – 3.074).

Even though the strength of association (or magnitude of the risk ratios) of statin use and incidence of diabetes was higher in this study (HR=2.75 and OR=2.82), the increase in the risk of diabetes that was associated with statin therapy, compared to no statin therapy, is consistent with those of several observational studies. Statin therapy was significantly associated with a 14 percent, 15 percent, 20 percent, and 48 percent increase in risk of incident diabetes in the Danaei et al. (HR=1.14, 95% C.I.=1.10 – 1.19),[518] Wang et al. (HR=1.15, 95% C.I.=1.08 – 1.22),[519] Zaharan et al. (HR=1.20, 95% C.I.=1.17 – 1.23),[520] and Culver et al. (HR=1.48, 95% C.I..=1.38 – 1.59)[521] studies, respectively.

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[518] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[519] Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."
[520] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

As mentioned earlier, the higher risk ratios observed in this present study compared to those of previous studies may be due to the fact that the pre-index period used in identifying occurrence of incident diabetes was limited to a period of six months (there was only two years of data available to work with in the database). Had a longer time frame of data been available, a longer pre-index period may have classified some incident diabetes cases as prevalent diabetes cases, and those cases would have been excluded from the study cohort. The current study had only six months of pre-index period (for identifying new users of statin and previous cases of diabetes) and a maximum 18 months of observation period. These periods were shorter compared to the 11 years of observation period and 2 years of pre-index period in the Danaei et al. study,[522] the 6 years of observation period in the Zaharan et al. study,[523] and the 4 years of observation period in the Wang et al. study.[524]

For similar reason, the magnitude of the risk ratios obtained for the association of each statin type and incidence of diabetes (discussed in the next section) might have been higher in this study compared to those obtained in previous studies.

Sensitivity Analysis

A sensitivity analysis was conducted to examine how varying lengths of the pre-index period affected the magnitudes of the risk ratios. Study results found in Appendix

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[521] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."
[522] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[523] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."
[524] Wang KL et al., "Statins, risk of diabetes, and implications on outcomes in the general population."

G shows that the magnitudes of the hazard and odds ratios decreased ‘slightly’ when the pre-index period for identifying prevalent diabetes cases was increased from six months to one year. In contrast, the magnitudes of the hazard and odds ratios decreased ‘substantially’ when the pre-index period for identifying prevalent diabetes cases was increased from six months to 1.5 years.

5.6 STATIN TYPES AND INCIDENCE OF DIABETES

Apart from examining the association of incident diabetes with statins as a class, the associations of each statin type (i.e., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) with incident diabetes were also examined. The magnitudes of the risk ratios (hazard ratio and odds ratio) obtained in this study were compared to values obtained for similar studies of statin use and incidence of diabetes. It was hypothesized that the use of each statin type will be associated with an increase in diabetes risk and all the hypotheses were supported; however, the magnitude of the risk ratios obtained in this study for each statin type was higher compared to those found in the literature.

As mentioned earlier, one reason the risk ratios might have been higher in this study may be due to misclassification of prevalent cases of diabetes as incident diabetes cases because of the limited pre-index data period used in identifying prevalent diabetes cases. However, since both the statin user group and the non-statin user group were both subjected to the same inclusion and exclusion criteria (for example, same six months of pre-index period for identifying and excluding prevalent cases of diabetes in both groups), it is possible that the risk ratios might still have been on the high side even if longer data periods were available.

The demographics of the study population and the kinds of variables controlled for in the regression analyses could also explain the discrepancies of the risk ratios obtained in this study compared to those of previous studies. Important diabetes risk

factors that would have been ideal to control for but were not available in the *MarketScan* data used for this study include race/ethnicity information, family history of diabetes, physical activity level, cholesterol level (HDL-C, LDL-C, TG), height and weight data (thus, BMI), and presence or absence of prediabetes. Some of these variables were controlled for in previous research.

With regards to one of the demographic characteristics that was controlled for in this study (i.e., age), it appears that the argument of differences in study population age do not support why the risk ratios were higher in this study. Since the risk of diabetes has been found to increase with age,[525] it will be expected that the risk of diabetes that was associated with statin use should be lower in this study compared to previous studies. The 2014 National Diabetes Statistics Report showed that diabetes prevalence is higher among people aged 65 years and older (25.9%) compared to those aged 45 – 64 years (16.2%) and 20 – 44 years (4.1%).[526] However, this hypothesis was not supported as the risk of diabetes was higher in our study even though the mean age of our study population was lower compared to the study population mean age of previous studies.

In addition, prevalence of diabetes has been shown to differ by race/ethnicity. The 2014 National Diabetes Statistics Report cited above also showed that the prevalence of diagnosed diabetes is higher among American Indians/Alaska Natives (15.9%) compared to among Hispanic blacks (13.2%), Hispanics (12.8%), Asian-Americans (9.0%) and

[525] Centers for Disease Control and Prevention, "National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014."
[526] Ibid.

non-Hispanic whites (7.6%).[527] However, we were not able to control for this important demographic factor. Only one study (Culver et al.) controlled for race/ethnicity among its study population.[528] Thus, the race/ethnicity argument may or may not explain why diabetes rates were higher in this study.

Perhaps the age and race/ethnicity arguments presented above lends more credence to the argument that the higher rates of diabetes as observed in this study may be due to the first reason proposed above (i.e., possibility of a misclassification error due to short data range). This might be compounded by the inability to account for some important diabetes risk factors (such as family history of diabetes, BMI and cholesterol levels) that were accounted for in some studies. Moreover, a handful of previous studies[529] accounted for about the same types of diabetes risk factors that were accounted for in our study but obtained risk ratios that were less than those obtained in this study.

Nevertheless, the following section discusses the association of each statin type and incidence of diabetes and how the risk ratios compares to those obtained in previous studies.

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[527] Ibid.

[528] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

[529] Carter AA et al., "Risk of incident diabetes among patients treated with statins: population based study."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

5.6.1 Atorvastatin Use and Incidence of Diabetes

Results from both the Cox regression and the logistic regression analyses indicated that atorvastatin therapy was significantly associated with increase an in risk of incident diabetes compared to non-statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among atorvastatin users was 2.425 times the hazard of incident diabetes among non-statin users (HR=2.425, 99% C.I.=2.200 – 2.673). The logistic regression analysis also indicated that the odds of incident diabetes among atorvastatin users was 2.485 times the odds of incident diabetes among non-statin users (OR=2.485, 99% C.I.=2.246 – 2.749).

The increase in risk of diabetes associated with atorvastatin therapy in this study is consistent (but with a higher risk ratio magnitude) compared to results of previous observational studies that found a statistically significant association between atorvastatin use and increase in risk of incident diabetes. The hazard ratios of these previous significant associations ranged from 1.22 – 1.61, as found in the Danaei et al. (HR=1.22, 95% C.I.=1.12 – 1.32),[530] Zaharan et al. (HR=1.25, 95% C.I.=1.21 – 1.28),[531] and Culver et al. (HR=1.61, 95% C.I.=1.26 – 2.06)[532] studies.

Differences in the magnitudes of the risk ratios obtained in this study compared to those of previous studies might be due to differences in study design. For example, Danaei et al. used primary markers such as LDL-C and HDL-C, and BMI to account for

[530] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[531] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."
[532] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

differences in subjects' cholesterol levels and obesity, respectively. This study used diagnoses of hyperlipidemia and obesity (which was underreported) as proxies for cholesterol levels and BMI, respectively. In addition, the Culver et al. study was a prospective cohort study of statin use in postmenopausal women and the study controlled for race/ethnicity, family history of diabetes, and physical activity. Our study was retrospective in nature, and controlled for some important diabetes risk factors that included gender and CCI score but not the other variables used in Culver's study.

However, the study result is consistent (with respect to the magnitude of the risk ratio) as those obtained in the Chen et al. case-control study.[533] That study reported that the odds of incident diabetes among atorvastatin users was 2.80 times the odds of incident diabetes among non-statin users (OR=2.80, 95% C.I.=1.74 – 4.49). The odds ratio for atorvastatin in this study was 2.485. The Chen et al. study was a population-based case-control study of the differential impact of statins on new-onset diabetes in 1,065 Taiwanese women with mean age of 61 years and their 10,650 matched-controls.[534] However, it is unclear why the odds ratio and the upper range of the 95% confidence interval of the odds ratio were high in the Chen et al. study compared to what was generally reported in the literature. Matching on important study variables as done in the Chen et al. study should have minimized differences between the groups. In addition,

[533] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."
[534] Ibid.

rates of obesity (a very important diabetes risk factor) are also lower among Asian population compared to other populations.[535]

Nevertheless, rather than a statistically significant increase in the risk of diabetes with atorvastatin therapy as found in the majority of previous studies, one study reported a protective effect of atorvastatin use against diabetes,[536] while other studies reported a non-statistically significant increase in risk of diabetes with atorvastatin use.[537]

[535] Finucane MM et al., "National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants."
[536] Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."
[537] Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

5.6.2 Fluvastatin Use and Incidence of Diabetes

Results from both the Cox regression and the logistic regression analyses indicated that fluvastatin therapy was significantly associated with an increase in risk of incident diabetes compared to non-statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among fluvastatin users was 2.064 times the hazard of incident diabetes among non-statin users (HR=2.064, 99% C.I.=1.647 – 2.586). The logistic regression analysis also indicated that the odds of incident diabetes among fluvastatin users was 2.161 times the odds of incident diabetes among non-statin users (OR=2.161, 99% C.I.=1.704 – 2.742).

The increase in the risk of diabetes associated with fluvastatin therapy in this study is consistent (but with a higher risk ratio magnitude) when compared to results of previous observational studies. Danaei et al. found a 2% increase in risk of diabetes associated with fluvastatin use (HR=1.02, 95% C.I.=0.69 – 1.50),[538] while Culver et al. found a 61% increase in risk of diabetes associated with fluvastatin use (HR=1.61, 95% C.I.=1.35 – 1.92).[539] As mentioned earlier (under atorvastatin), differences in the magnitudes of the risk ratios obtained in our study compared to these studies might be due to differences in study design and whether certain independent risk factors for diabetes were accounted for in the regression analyses. Moreover, rather than a statistically significant increase in diabetes risk with fluvastatin therapy that was

[538] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."
[539] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

observed in many studies, some studies reported a protective effect of fluvastatin use against diabetes,[540] while the increase in risk of diabetes with fluvastatin use was not statistically significant in another study.[541]

[540] Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."
[541] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

5.6.3 Lovastatin Use and Incidence of Diabetes

Results from both the Cox regression and the logistic regression analyses indicated that lovastatin therapy was significantly associated with an increase in risk of incident diabetes compared to non-statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among lovastatin users was 3.413 times the hazard of incident diabetes among non-statin users (HR=3.413, 99% C.I.=2.949 – 3.951). The logistic regression analysis also indicated that the odds of incident diabetes among lovastatin users was 3.565 times the odds of incident diabetes among non-statin users (OR=3.565, 99% C.I.=3.051 – 4.165).

The increase in risk of diabetes associated with lovastatin therapy in this study is consistent (but with a higher risk ratio magnitude) when compared to previous research. Ma et al. found a 36% increase in risk of diabetes associated with lovastatin use (HR=1.36, 95% C.I.=1.24 – 1.48),[542] while Culver et al. found a 35% increase in risk of diabetes associated with lovastatin use (HR=1.35, 95% C.I.=1.19 – 1.55).[543]

While similar kinds of variables were controlled for in our study and the Ma et al. study, the magnitude of the risk ratio was higher in our study even though differences were minimized between the groups by controlling for CCI score, obesity (though, underreported), and hyperlipidemia – variables that were not controlled for in the Ma et al. study. One explanation could be that our study used data from the United States while

[542] Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."
[543] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

the Ma et al. study comprised of subjects from an Asian country (Taiwan). The US population may be different than the Asian population in terms of the prevalence of diabetes risk factors such as overweight and obesity. Studies indicate that the US has the highest rate of obesity among all high income population of North America and Europe.[544] This is in contrast to people from East Asian countries who have mean BMIs that are among the lowest in the world.[545]

[544] Finucane MM et al., "National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants."
[545] Ibid.

5.6.4 Pravastatin Use and Incidence of Diabetes

Results from both the Cox regression and the logistic regression analyses indicated that pravastatin therapy was significantly associated with an increase in risk of incident diabetes compared to non-statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among pravastatin users was 1.889 times the hazard of incident diabetes among non-statin users (HR=1.889, 99% C.I.=1.620 – 2.202). The logistic regression analysis also indicated that the odds of incident diabetes among pravastatin users was 1.952 times the odds of incident diabetes among non-statin users (OR=1.952, 99% C.I.=1.663 – 2.290).

The increase in risk of diabetes associated with lovastatin therapy in this study is consistent (and within the same magnitude) with results of two observational studies. Ma et al. found a 30% increase in risk of diabetes associated with pravastatin use (HR=1.30, 95% C.I.=1.13 – 1.56),[546] while Culver et al. found a 63% increase in risk of diabetes associated with pravastatin use (HR=1.63, 95% C.I.=1.43 – 1.87).[547]

However, the study result was inconsistent with respect to the magnitude of the risk ratio found in the Chen et al. case-control study. The Chen et al. study reported that the odds of incident diabetes among pravastatin users was 3.41 times the odds of incident diabetes among non-statin users (OR=3.41, 95% C.I.=1.66 – 7.04).[548] The odds ratio in this study was 1.95. The fact that the Chen et al. study was conducted only among

[546] Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."
[547] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."
[548] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."

women from an Asian country (Taiwan) couldn't possibly explain why the magnitude of the odds ratio in the Chen et al. study was high compared to results of every study on this topic. Perhaps, there was statistical inefficiency as a result of the 1:10 case to control matching.

Furthermore, rather than a statistically significant increase in risk, one study reported a protective effect of pravastatin use against diabetes,[549] while the increases in risk of diabetes that were associated with pravastatin use were not statistically significant in some studies.[550]

[549] Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

[550] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."; Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

5.6.5 Rosuvastatin Use and Incidence of Diabetes

Results from both the Cox regression and the logistic regression analyses indicated that rosuvastatin therapy was significantly associated with an increase in risk of incident diabetes compared to non-statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among rosuvastatin users was 1.615 times the hazard of incident diabetes among non-statin users (HR=1.615, 99% C.I.=1.307 – 1.996). The logistic regression analysis also indicated that the odds of incident diabetes among rosuvastatin users was 1.495 times the odds of incident diabetes among non-statin users (OR=1.495, 99% C.I.=1.199 – 1.865).

The increase in risk of diabetes associated with rosuvastatin therapy in this study is consistent (and within the same magnitude) with the results of an observational study that found a statistically significant association between rosuvastatin use and increase in risk of incident diabetes. Zaharan et al. found a 42% increase in risk of diabetes associated with rosuvastatin use (HR=1.42, 95% C.I.=1.33 – 1.52).[551] The hazard ratio obtained in this study was 1.62 (a 62% increase in risk).

However, just like the risk ratios obtained for atorvastatin and pravastatin, the magnitude of the risk ratio obtained for rosuvastatin in the Chen et al. study was inconsistent with those obtained in this and other studies. The Chen et al. study reported that the odds of incident diabetes among rosuvastatin users was 4.69 times the odds of

[551] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."

incident diabetes among non-statin users (OR=4.69, 95% C.I.=2.78 – 7.92).[552] The odds ratio for rosuvastatin was 1.49 in this study. Even though the Chen et al. study used a case-control design to examine statin use and the risk of diabetes among Asian women while our study used a retrospective cohort design to examine the use of statins and incidence of diabetes among American men and women, it is difficult to speculate what could be responsible for the stark differences in risk ratio magnitudes between the Chen et al. study, our study, and similar studies on the topic.

Nevertheless, rather than reporting a statistically significant increase in risk of diabetes with rosuvastatin therapy, some studies have reported a protective effect of rosuvastatin use against diabetes,[553] while one study reported a non-statistically significant increase in diabetes risk with rosuvastatin use.[554]

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[552] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."
[553] Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."; Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."
[554] Danaei G et al., "Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival."

5.6.6 Simvastatin Use and Incidence of Diabetes

Results from both the Cox regression and the logistic regression analyses indicated that simvastatin therapy was significantly associated with an increase in risk of incident diabetes compared to non-statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among simvastatin users was 2.567 times the hazard of incident diabetes among non-statin users (HR=2.567, 99% C.I.=2.284 – 2.884). The logistic regression analysis also indicated that the odds of incident diabetes among simvastatin users was 2.651 times the odds of incident diabetes among non-statin users (OR=2.651, 99% C.I.=2.347 – 2.994).

The increase in risk of diabetes associated with simvastatin therapy in this study is consistent (but with a higher risk ratio magnitude) compared to results of previous observational studies. The risk ratios of these previous significant associations ranged from 1.10 – 1.41, as found in the Danaei et al. (HR=1.14, 95% C.I.=1.09 – 1.20),[555] Zaharan et al. (HR=1.14, 95% C.I.=1.06 – 1.23),[556] Ma et al. (HR=1.30, 95% C.I.=1.14 – 1.47),[557] and Culver et al. (HR=1.10, 95% C.I.=1.04 – 1.17)[558] studies. As mentioned earlier, differences in the magnitudes of the risk ratios obtained in our study compared to these previous studies could be due to differences in the demographics of the study population and differences in study design.

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[555] Ibid.
[556] Zaharan NL et al., "Statins and risk of treated incident diabetes in a primary care population."
[557] Ma T et al., "The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study."
[558] Culver AL et al., "Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

Similar to atorvastatin, pravastatin, and rosuvastatin therapies, the magnitude of the risk ratio obtained for simvastatin was higher in the Chen et al. study compared to what was obtained in this study. The Chen et al. study reported that the odds of incident diabetes among simvastatin users was 4.09 times the odds of incident diabetes among non-statin users (OR=4.09, 95% C.I.=2.92 – 6.64).[559] The odds ratio for simvastatin was 2.65 in this study. However, the increase in diabetes risk that was associated with simvastatin use was not statistically significant in some studies.[560]

[559] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."
[560] Ma T et al., "Statins and new-onset diabetes: a retrospective longitudinal cohort study."; Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."

5.7 INTENSIVE-DOSE STATIN USE AND INCIDENCE OF DIABETES

In addition to examining the risk of diabetes associated with use of statins as a class and with each statin type, it was imperative to examine how statin dosage intensities influenced the risk of diabetes among statin users. Some studies have suggested that the risk of diabetes is higher with high potency, high dose (i.e., intensive-dose) statin therapies such as atorvastatin 40 and 80mg, rosuvastatin 20 and 40mg, and simvastatin 80mg compared to moderate/high potency and low/moderate dose (i.e., moderate-dose) statin therapies such as atorvastatin 10 and 20mg, rosuvastatin 5 and 10mg, simvastatin 5, 10, 20, and 40mg, and all doses of fluvastatin, pravastatin, and lovastatin.[561]

Results from both the Cox regression and the logistic regression analyses indicated that intensive-dose statin therapy was significantly associated with an increase in risk of incident diabetes compared to moderate-dose statin therapy. The Cox regression analysis indicated that the hazard of incident diabetes among intensive-dose statin users was 1.525 times the hazard of incident diabetes among moderate-dose statin users (HR=1.525, 99% C.I.=1.378 – 1.686). The logistic regression analysis also indicated that the odds of incident diabetes among intensive-dose statin users was 1.578 times the odds of incident diabetes among moderate-dose statin users (OR=1.578, 99% C.I.=1.414 – 1.761).

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[561] LaRosa JC et al., "Intensive lipid lowering with atorvastatin in patients with stable coronary disease."; Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

Only one observational study had examined the association between statin dosage intensity and incidence of diabetes.[562] The increase in risk of diabetes associated with intensive-dose statin therapy in our study is not consistent compared to what was found in this previous observational study. The Ko et al. study examined the occurrence of diabetes mellitus in 8,540 hospitalized patients (mean age=78 years) with myocardial infarction and their 8,540 matched-pair controls who were prescribed intensive-dose and moderate-dose statins. Study results suggests that at 5 years, there was no statistically significant difference (p=0.19) in the proportion of intensive-dose statin patients (13.6%) and moderate-dose statin patients (13.0%) that had new onset diabetes.[563] In comparison, the results of our univariate analysis showed that the proportion of intensive-dose statin users that had incident diabetes (13.4%) was significantly higher than the proportion of moderate-dose statin users (9.3%) that had incident diabetes (χ^2=103.4; df=1, p<0.0001).

However, the results of this study is consistent with results from a randomized control trial (RCT)[564] and a study involving meta-analysis of five RCTs.[565] These studies suggests that there is an increased risk of diabetes among intensive-dose statin user compared to moderate-dose statin users. Meanwhile, many researchers have argued that the lipid-lowering effects and the larger cardiovascular benefit gained from using high potency, high dose statins far outweigh the potential increase in risk of new onset

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562 Ko DT et al., "Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins."
563 Ibid.
564 LaRosa JC et al., "Intensive lipid lowering with atorvastatin in patients with stable coronary disease."
565 Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

diabetes associated with such intensive-dose statins.[566] Moreover, increases in diabetes risk that was associated with intensive-dose statin use were not statistically significant in many RCTs.[567] It is worth noting that the primary interest of these RCTs was not to measure the risk of diabetes. These RCTs were designed essentially to examine the superiority of the lipid-lowering effect of higher statin dosages over moderate or usual statin dosages.

Even though it is unclear how intensive-dose statin use may increase the risk of new onset diabetes compared to moderate-dose statin use, several plausible hypotheses has been advanced. These hypotheses include the potency hypothesis,[568] and effects related to the hydrophilic/lipophilic nature of each statin.[569] The potency hypothesis suggests that more side effects (including diabetes occurrence) might be associated with higher potency statins compared to lower potency statins. Furthermore, due to the utilization of different transport systems that may lead to varying degrees of intercellular

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566 Jones PH et al., "Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial)."; Jones P, Kafonek S, Laurora I, and Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). Ibid.1998;81(5):582-7; Betteridge J, "Pitavastatin - results from phase III & IV."; Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

567 Cannon CP et al., "Intensive versus moderate lipid lowering with statins after acute coronary syndromes."; de Lemos JA et al., "Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial."; Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. Ibid.2005;294(19):2437-45; Armitage J et al., "Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial."

568 Navarese E, Szczesniak A, Kolodziejczak M, Gorny B, Kubica J, and Suryapranata H. Statins and risk of new-onset diabetes mellitus: Is there a rationale for individualized statin therapy? Am J Cardiovasc Drugs. 2014;14(2):79-87.

569 Dormuth CR, Filion KB, Paterson JM, et al. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. Vol 348. ed.: 2014.

concentrations of the statin,[570] the hydrophilic/lipophilic hypothesis posits that more adverse effects may be associated with lipophilic statins compared to hydrophilic statins. Interestingly, the results of this study does not seem to support the potency hypothesis because the risks of diabetes (as evidenced by the magnitudes of the hazard ratios) were not consistently higher among high potency statins such as atorvastatin (HR=2.42), rosuvastatin (HR=1.62), and simvastatin (HR=2.57) compared to low/moderate potency statins such as fluvastatin (HR=2.06), lovastatin (HR=3.41), and pravastatin (HR=1.88).

However, the hydrophilic/lipophilic hypothesis appears to be supported by our results because the magnitudes of the hazard ratios for hydrophilic statins such as pravastatin (HR=1.88) and rosuvastatin (HR=1.61) were consistently lower compared to the magnitudes of the hazard ratios associated with lipophilic statins such as atorvastatin (HR=2.43), fluvastatin (HR=2.06), lovastatin (HR=3.41), and simvastatin (HR=2.57). The higher risks of diabetes associated with lipophilic statins might be explained by their higher potential to reduce adiponectin hormone and increase insulin resistance compared to hydrophilic statins.[571]

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[570] Bitzur R, Cohen H, Kamari Y, and Harats D. Intolerance to statins: mechanisms and management. Diabetes Care. 2013;36 Suppl 2:S325-30.

[571] Dormuth CR et al., *Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases*, 348.

5.8 COMPARISON OF THE RISK OF DIABETES AMONG USERS OF DIFFERENT STATIN TYPES

One of the main study objectives was to estimate the risk of diabetes for users of each statin type (i.e., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin). In order to be consistent, a common group was chosen as the comparison group. Thus, users of each statin type were compared to non-statin users and the risk ratio (i.e., hazard ratio or odds ratio) associating the use of each statin with new onset diabetes was estimated. From the results, lovastatin users (HR=3.41, OR=3.57) had the highest risk of new onset diabetes and were followed, consecutively, by users of simvastatin (HR=2.57, OR=2.65), atorvastatin (HR=2.43, OR=2.49), fluvastatin (HR=2.06, OR=2.16), and pravastatin (HR=1.89, OR=1.95). Rosuvastatin users (HR=1.62, OR=1.50) had the least risk of new onset diabetes among all statin users.

As mentioned earlier, the potency hypothesis (which correlates higher potencies with higher side effects) does not seem to explain why the risks of diabetes was highest among lovastatin, simvastatin, atorvastatin, and fluvastatin users since it will be expected that higher potency statins such as atorvastatin, rosuvastatin, and simvastatin should consistently have higher risk ratios compared to lower potency statins such as lovastatin and fluvastatin. However, the lipophilic/hydrophilic hypothesis may explain why users of lipophilic statins such as atorvastatin, fluvastatin, lovastatin, rosuvastatin, and simvastatin all had higher risks of diabetes compared to users of hydrophilic statins such as pravastatin and rosuvastatin.

It has been hypothesized that lipophilic and hydrophilic statins have differential effects on adiponectin and insulin resistance.[572] Adiponectin is a hormone that decreases gluconeogenesis (i.e., endogenous production of glucose from non-carbohydrate substrates and the target of antidiabetic drug such as metformin) and increases glucose uptake. One study showed a correlation between high blood levels of adiponectin and reduction in the risk of type 2 diabetes.[573] Simvastatin – a lipophilic statin – has been shown to significantly reduce both insulin sensitivity and adiponectin levels in patients with hypercholesterolemia.[574] In contrast, one study showed that pravastatin, a hydrophilic statin, had less deleterious effects on levels of adiponectin and insulin sensitivity.[575]

Other postulated mechanisms by which statins may induce new onset diabetes include down-regulation of the pancreatic beta-cell function,[576] suppression of ubiquinone (CoQ_{10}) biosynthesis,[577] promotion of beta-cell apoptosis (cell death),[578] and

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572 Ibid.

573 Spranger J, Kroke A, Mohlig M, et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet. 2003;361(9353):226-8.

574 Koh KK, Quon MJ, Han SH, et al. Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients. Diabetes Care. 2008;31(4):776-82.

575 Koh KK, Quon MJ, Han SH, et al. Differential metabolic effects of pravastatin and simvastatin in hypercholesterolemic patients. Atherosclerosis. 2009;204(2):483-90.

576 Ibid.

577 Mabuchi H et al., "Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients."

578 Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, and Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. Diabetologia. 2006;49(8):1881-92.

impairment of glucose transport.[579] Atorvastatin and lovastatin, both lipophilic statins, have been shown to impair glucose transportation by suppression of isoprenoid synthesis, which in turn decreases the expression of insulin-responsive glucose transporter type (GLUT)-4.[580]

Evaluation of current observational studies of statin use and incidence of diabetes appear to suggest that simvastatin and atorvastatin had the greatest potential to be significantly associated with increased risk of incident diabetes, while fluvastatin and lovastatin had the least potential to be significantly associated with an increase in risk. Pravastatin and rosuvastatin appear to have moderate potential to be significantly associated with increased risk of diabetes. This observation is partly consistent with our results which showed that lovastatin, simvastatin, atorvastatin, and fluvastatin (all statins with HR or OR >2) had the strongest association with incident diabetes while fluvastatin, pravastatin, and rosuvastatin had moderate associations with incident diabetes.

[579] Ibid.; Chamberlain LH. Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes. FEBS Lett. 2001;507(3):357-61.
[580] Chamberlain LH, "Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes."; Nakata M et al., "Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control."

5.9 COMPARISON OF THE RESULTS OF THE COX AND LOGISTIC REGRESSION ANALYSES

This study utilized a retrospective cohort design to investigate the association of statin therapy and increased risk of new onset diabetes. To achieve this purpose, two kinds of dependent variables were defined as measures for diabetes. The first measure was survival time, and it was defined as the time between receipt of the index medication and manifestation of diabetes. A group with the shorter survival time may be more likely to be at an increased risk of the disease. Because survival time is continuous in nature and there were censored data, the Cox proportional hazard regression analysis was appropriate to estimate the hazard ratio of diabetes between the active group (i.e., users of statins as a class and users of each statin type) and the reference group (i.e., non-statin users). Hazard ratios above 1.0 means that the active group has a higher hazard for diabetes compared to the reference group.

Furthermore, incidence of diabetes was used as the second measure for diabetes. It is a dichotomous variable (yes/no) that either indicates the presence or absence of new onset diabetes among the two groups that are being compared. Because of the dichotomous nature of this variable and because other covariates will be controlled for, a binary logistic regression analysis was appropriate. Similar to the hazard ratio in Cox regression, an odds ratio was calculated to measure the odds of diabetes among the active group compared to the odds of diabetes among the reference group. Odds ratios above 1.0

also means that the active group has a higher odds of diabetes compared to the reference group.

The premise for conducting two different statistical analyses was for the results of one analysis to validate the results of the other (given two different forms of dependent variables in each analysis). The results of the two statistical analyses were expected to be consistent and comparable in terms of the magnitude and direction of the hazard and odds ratios.

Study results from both the Cox and logistic regression analyses indicated that there was consistency in the magnitude and direction of the estimated hazard and odds ratios. For example, the hazard and odds ratios (i.e., HR=2.75, OR=2.82) associating statin use with incident diabetes were consistent and approximately equal. Similarly, compared to no statin use, the hazard and odds ratios for the use of atorvastatin (HR=2.43, OR=2.49), fluvastatin (HR=2.06, OR=2.16), lovastatin (HR=3.41, OR=3.57), pravastatin (HR=1.89, OR=1.95), rosuvastatin (HR=1.62, OR=1.50), and simvastatin (HR=2.57, OR=2.65) were consistent and approximate values of each other. There was also consistency of the risk ratios comparing intensive-dose statin users to moderate-dose statin users (HR=1.53, OR=1.58).

The magnitudes of the hazard and odds ratios obtained in this study might have been consistent, approximate values of each other because the study design (retrospective cohort) was the same even though two different statistical analyses were employed. Similar to the results of this study, there was consistency in the magnitudes of the hazard

and odds ratio obtained in one study that employed a retrospective cohort design but used two different statistical analyses (i.e., Cox and logistic regression) to evaluate the hazard and odds of incidence of type 2 diabetes that was associated with the use of antidepressants.[581] The value of the hazard and odds ratios in that study was 1.56 and 1.49, respectively. In concordance, hazard and odds ratios of 2.75 and 2.82, respectively, were associated with statin use and incidence of diabetes in this study.

Perhaps, differences and/or concordance in the magnitude and direction of the hazard and odds ratios are more dictated by the type of study design implemented rather than the statistical analysis employed (though the latter is often dictated by the former). For example, results of previous observational studies suggest that the magnitudes of the risk ratios appear to be higher for case-control studies (mostly analyzed using logistic regression) than for prospective or retrospective cohort studies (mostly analyzed using Cox regression). The magnitudes of the hazard ratios in cohort studies of statin use and incidence of diabetes ranged from 0.77 – 1.61 (atorvastatin), 0.46 – 1.61 (fluvastatin), 0.70 – 1.36 (lovastatin), 1.01 – 1.63 (pravastatin), 0.54 – 1.42 (rosuvastatin), and 1.10 – 1.41 (simvastatin). The lower magnitude of these hazard ratios are in contrast to the high magnitude of the odds ratios associated with the use of atorvastatin (OR=2.80), pravastatin (OR=3.41), rosuvastatin (OR=4.69), and simvastatin (OR=4.09) in the Chen et al. case-control study.[582] Nevertheless, the lower risk ratios obtained in cohort studies

[581] Khoza S, "Use of antidepressant agents and the incidence of type 2 diabetes mellitus: A methodological comparison."; Khoza S et al., "Use of antidepressant agents and the risk of type 2 diabetes."
[582] Chen CW et al., "Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an Asian country."

were not consistently supported as low odds ratios were also associated with the use of pravastatin (OR=0.70) and simvastatin (OR=1.00) in the Jick et al. case-control study.[583]

It should be noted, however, that odds ratios are more appropriate for estimating risk ratios in case-control studies but are considered less appropriate for cohort studies where the relative risk may be overestimated especially when the event is frequent.[584] This observation was supported in the results of this retrospective cohort study where the values of the odds ratios were consistently higher (but of comparable magnitude) than the values of the hazard ratios.

[583] Jick SS and Bradbury BD, "Statins and newly diagnosed diabetes."
[584] Deeks J. When can odds ratios mislead? : Odds ratios should be used only in case-control studies and logistic regression analyses. BMJ : British Medical Journal. 1998;317(7166):1155-55.

5.10 STUDY STRENGTHS AND LIMITATIONS

Before discussing the limitations of the current study, it is worthwhile to acknowledge some of its merits. First, the large *MarketScan* database used for this study ensured that the study was adequately powered to detect significant associations between statin use and incident diabetes if they truly existed. Second, the study used two different statistical approaches to estimate the risks of diabetes associated with statin use. This is the first observational study of statin use and incidence of diabetes that utilized this approach. Third, accuracy of disease ascertainment was increased by the use of ICD-9-CM codes instead of proxies such as medication use. Fourth, this study is among the few observational studies that used real-world data to evaluate the influence of high statin dosage intensity on the risk of new-onset diabetes. The current ATP IV cholesterol guidelines advocates for more aggressive management of LDL-C and ASCVD by using high dose statins. This new guideline has implications for those using statins for primary prevention who may be at higher risk of diabetes than the cardiovascular gains of statin therapy. Lastly, the validity of the study results was increased by the ability to control for some important risk factors that would have increased the risk of diabetes for one group compared to the other, independent of the use of statin. Of note was the possibility to control for confounding by indication (i.e., the premise that hyperlipidemia – the indication for which statins are used – was responsible for the increase in diabetes risk rather than the statin itself).

Despite these study strengths, it is important that the study results be interpreted bearing in mind the study limitations. One of the main study limitations was the possibility of disease misclassification. Because the data were limited to two years in length, only a six-month pre-index period was used to identify and exclude prevalent diabetes cases. This has the potential to increase diabetes incidence among the study population (this hypothesis was confirmed by a sensitivity analysis found in Appendix G where longer pre-index periods resulted in lower diabetes incidence and risk ratios). However, this limitation might be attenuated by the fact that both statin users and non-statin users were equally exposed to the same sets of study inclusion and exclusion criteria. In addition, only one diabetes diagnosis served as the proxy for classifying subjects as having diabetes mellitus. Using two or more diabetes diagnosis could decrease disease misclassification. Future studies should evaluate the association between statin therapy and incidence of diabetes using longer data periods and more robust definitions of the disease.

Second, some critical variables were not available in the dataset. These include variables such as race/ethnicity, family history of diabetes, physical activity level, cholesterol level, body mass index, smoking status, diet, and presence or absence of prediabetes. All of these factors could be associated with an increased risk of diabetes that is independent of the use of statins. It is possible that higher risk of diabetes (compared to what is reported in the literature) that was associated with statin use as found in this study might be due to not accounting for these variables. In addition, the

prevalence of obesity diagnosis recorded among the study population was low compared to the prevalence of obesity among adult US population. Even though this variable was accounted for in the analyses, it is possible that the variable may not have been adequately accounted for as obesity might be more prevalent among statin users compared to non-statin users. Future observational studies should control for these important variables that could be responsible for the increased risk of diabetes, irrespective of statin therapy.

Third, even though the data integrity of the *MarketScan* data is very high, it is nevertheless not immune from limitations surrounding claims databases. There is the possibility of missing data, errors in data coding (i.e., over/under-coding of ICD-9-CM codes), and exclusion of subjects due to eligibility changes for insurance programs. For example, the data used for this study did not include people who were 65 years and older. Bias could be introduced because older people may have more comorbidities and risk factors for diabetes.

Finally, the *MarketScan* Database that was used for this study used data collected in 2003 – 2004. Due to changes in statin prescribing and utilization pattern, there is a possibility that study results might be different if current data were applied. In addition, the *MarketScan Commercial Claims and Encounters Database* used for this study is a convenience sample that may not generalized well to other US populations. This is because the data were sourced mainly from large employers which have private insurance. Small and medium-sized firms were underrepresented in the dataset. Thus, this

study's population may be different from other groups such as the Medicaid (predominantly females and low socio-economic status), Medicare (predominantly older with more disease comorbidities) and uninsured populations.

5.11 STUDY IMPLICATIONS

The main objective of this study was to assess whether statin therapy was associated with an increase in risk of new onset diabetes. This study confirmed the hypothesis that statin therapy is associated with an increase in risk of incident diabetes and helped fill some gaps in the literature because there are few observational studies examining this phenomenon using US-based data. The results of the study revealed the following about statin use:

1) The hazard and odds of incident diabetes increased significantly by almost three-fold in patients receiving statins compared to patients not receiving statin therapy.

2) Compared to patients receiving no statin therapies, the hazard and odds of incident diabetes increased significantly by about two-fold in patients receiving all types of statins, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. The risk of diabetes was highest among lovastatin users and lowest among rosuvastatin users.

3) The hazard and odds of incident diabetes increased significantly by about one and one-half-fold in patients receiving intensive-dose statins compared to those receiving moderate-dose statins.

Although statins are generally safe and well tolerated, this study and several other studies have suggested that statins are associated with a moderate increase in risk of new-onset diabetes. These previous observations prompted the FDA to revise statin labels to now include a warning of an increased risk of incident diabetes mellitus as a result of

increases in glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG).[585] Even though the precise pathway by which statins induce incident diabetes is still unclear, statins are thought to worsen glycemic control and increase fasting plasma glucose and insulin resistance, thereby possibly leading to diabetes mellitus.[586]

Because cardiovascular disease is a major cause of mortality and morbidity in America and around the world, several researchers have debated whether the larger cardiovascular benefits gained from using statins (including the use of intensive doses) far outweigh the potential increase in risk of new onset diabetes that is associated with statin therapy. Several landmark statin trials and meta-analyses of statin RCTs have demonstrated the beneficial effects of statins in primary and secondary prevention of cardiovascular disease. The meta-analysis study by Sattar et al. indicated that statin therapy was associated with 5.4 fewer deaths from CHD and non-fatal MI per 255 patients treated over 4 years. This is in contrast to only one additional case of new onset diabetes recorded per 255 patients treated with statins.[587] Preiss et al. conducted a meta-analysis of five statin RCTs comprising 32,752 patients who were prescribed intensive-dose and moderate-dose statins.[588] The study found that while only two additional cases

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585 Food and Drug Administration, "FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs".

586 Sukhija R et al., "Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients."; Mabuchi H et al., "Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients."; Sasaki J, Iwashita M, and Kono S. Statins: beneficial or adverse for glucose metabolism. Ibid.2006;13(3):123-9.

587 Sattar N et al., "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials."

588 Preiss D et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis."

of incident diabetes were recorded, intensive-dose statin therapy was associated with 6.5 fewer cardiovascular events. This translates into a lesser number needed to treat of 155 for cardiovascular events compared to a larger number needed to harm of 498 for new-onset diabetes. Thus, these studies argue that there is little controversy regarding the beneficial effects of statins in secondary prevention of cardiovascular diseases.

However, there has been controversy as to whether the absolute benefits of statins in primary prevention far outweigh the risk of development of diabetes, especially among low-risk patients without a history of cardiovascular disease.[589] This controversy was heightened by the December 2013 release of the American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol (colloquially, ATP IV guidelines).[590] Among others, this new guideline recommends statin therapy (including the use of intensive doses) for individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C of 70 – 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher.

Compared to the ATP III guidelines, some physicians believe that the new ATP IV guidelines will expand statin use to millions of patients. This is because the LDL-C (for example, LDL-C of 70 – 100mg/dL were often considered 'normal levels') and the ASCVD risk thresholds were considered too low and several millions of people (who may be truly at low risk of cardiovascular diseases and might not need statins) were

[589] Navarese E et al., "Statins and risk of new-onset diabetes mellitus: Is there a rationale for individualized statin therapy?."
[590] Stone NJ et al., "2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."

easily categorized as high risk on the basis of their age, race, and smoking status – demographic and clinical factors that disproportionately increase the estimated 10-year ASCVD risk even in people with the so-called 'normal' LDL-C levels.

Thus, if there is a possibility that several million people are needlessly being treated with statins for primary prevention; then, there is an equal chance that several million people may also be potentially at risk for new-onset diabetes by the reason of their statin therapy. A Cochrane review of the benefit and risk associated with statin use in primary prevention noted that even though statin therapy significantly reduced all-cause cardiovascular mortality, the absolute benefits were very small – 1,000 people will have to be treated for one year to prevent one cardiovascular death.[591] Thus, the merits of statin therapy may be minimal among people with low cardiovascular risk as a higher 'number needed to treat' may be needed to gain marginal benefits. Furthermore, one author believed that the exact point at which cardiovascular benefits begins to outweigh the risk of diabetes among primary prevention patients may still be unclear.[592]

Therefore, in conjunction with the new ATP IV guidelines, it might be important for physicians to individualize statin therapy, especially among people with low cardiovascular risk. This tailored therapy should be based on sound clinical judgment, the patient's overall cardiovascular risk and metabolic profile, and the type and dose of statin

[591] Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.
[592] Navarese E et al., "Statins and risk of new-onset diabetes mellitus: Is there a rationale for individualized statin therapy?."

used.[593] Within the tailored therapy framework, the specific type and dose of statin used may be crucial. This is because different types and doses of statin vary in their ability to reduce LDL-C as well as in their diabetogenic potentials. Identifying patients who would benefit more from less diabetogenic statin types could help optimize the treatment by providing the highest benefit achievable while reducing the number of patients developing diabetes under statin therapy.

Despite its lower cost and potential to reduce LDL-C, and its being marginalized by newer, higher potency, and more advertised statins, one author suggests that pravastatin seems to be the least diabetogenic statin currently available on the market and it could be the ideal statin for patients with hyperlipidemia who have a low risk of cardiovascular disease but who have a high predisposition for diabetes.[594] The results of this study also support this argument as the risk of diabetes was lowest among pravastatin and rosuvastatin users.

Despite the association of statin use with incident diabetes, it is important to remember that statin therapy alone cannot possibly account for all the new cases of diabetes diagnosed during anti-hyperlipidemic therapy. The hazard and odds of development of new-onset diabetes may also be significantly accounted for by baseline diabetes risk factors that include increasing age, and clinical comorbidities such as

[593] Ibid.
[594] Ibid.

obesity, hyperlipidemia, and hypertension.[595] More long-term prospective RCTs and cost-effectiveness research may be needed to examine the benefit/risk ratios of statins, especially in the area of primary prevention.

[595] Waters DD, Ho JE, Boekholdt SM, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. J Am Coll Cardiol. 2013;61(2):148-52.

5.12 CONCLUSION

In conclusion, the results of the study lend support to the hypothesis that statin therapy is significantly associated with increase in the risk of new-onset diabetes. This increased risk was found not only in the use of statins as a class, but each statin type was also significantly associated with an increase in risk of incident diabetes mellitus. Furthermore, risk of diabetes was significantly increased in those that used intensive statin doses.

The recently released ATP IV cholesterol guideline advocates for the aggressive control of LDL-C in people with clinical evidence of ASCVD as well as in individuals without clinical evidence of ASCVD or diabetes who may be at increased risk of coronary heart disease by virtue of their age, cholesterol levels and estimated 10-year ASCVD risk. Even though a preponderance of the literature argues that the benefits of using statins in secondary prevention outweighs the potential for increase in risk of diabetes, there may be less confidence about the benefits of using statins among those with 'normal' LDL-C levels who do not have evidence of clinical ASCVD or diabetes and who may thus be more exposed to diabetes risks than the cardiovascular benefits gained.

Nevertheless, health care professionals can use targeted approach to optimize the management of their patient's hyperlipidemia. They can do this by using better clinical judgments to identify patients who would benefit more from less diabetogenic statin

types, thus providing the highest benefit achievable while reducing the number of patients developing diabetes under statin therapy.

APPENDICES

APPENDIX A

Results of Normality Testing

Tables A.1 and A.2 shows the summary statistics for the continuous dependent variables age, CCI score, MPR, diabetogenic medications (i.e., number of prescriptions for all diabetogenic medications and number of prescriptions for each diabetogenic medication), while Figures A.1 – A.10 shows the corresponding histograms (with normality curves) for these variables, respectively.

Table A.1: Summary Statistics for Age, Comorbidity Index Score, MPR, and Diabetogenic Medications				
	Age	**CCI score**	**MPR**	**Diabetogenic Medications[a]**
N Valid	116,224	116,224	50,557	116,224
Missing	0	0	7,555	0
Mean (SD)	46.42 (11.61)	0.15 (0.73)	75.0 (25.3)	3.24 (7.12)
Median	49	0	83.3	0
Skewness (SE)	-0.64 (0.007)	8.15 (0.007)	-0.89 (0.011)	3.16 (0.007)
Kurtosis (SE)	-0.49 (0.014)	80.35 (0.014)	-0.29 (0.022)	14.07 (0.014)
Minimum	20	0	0.2	0
Maximum	63	15	100	107

Abbreviation: MPR, medication possession ratio; SD, standard deviation; SE, standard error.
[a]Number of prescriptions for all diabetogenic medications.

Table A.2: Summary Statistics of Number of Prescriptions for Each Diabetogenic Medication						
	Thiazides	**Beta-blockers**	**Anti-psychotics**	**Anti-depressants**	**Immuno-suppressants**	**Gluco-corticoids**
N Valid	116,224	116,224	116,224	116,224	116,224	116,224
Missing	0	0	0	0	0	0
Mean (SD)	0.42 (2.15)	1.23 (3.78)	0.07 (0.99)	1.49 (4.50)	0.03 (0.80)	0.003 (0.09)
Median	0	0	0	0	0	0
Skewness (SE)	6.17 (0.007)	3.38 (0.007)	19.73 (0.007)	4.13 (0.007)	38.22 (0.007)	64.76 (0.007)
Kurtosis (SE)	41.99 (0.014)	11.48 (0.014)	510.25 (0.014)	22.74 (0.014)	1,796.15 (0.014)	5,429.19 (0.014)
Minimum	0	0	0	0	0	0
Maximum	37	38	50	94	64	9.93

Figure A.1: Histogram (with normality plot) for age

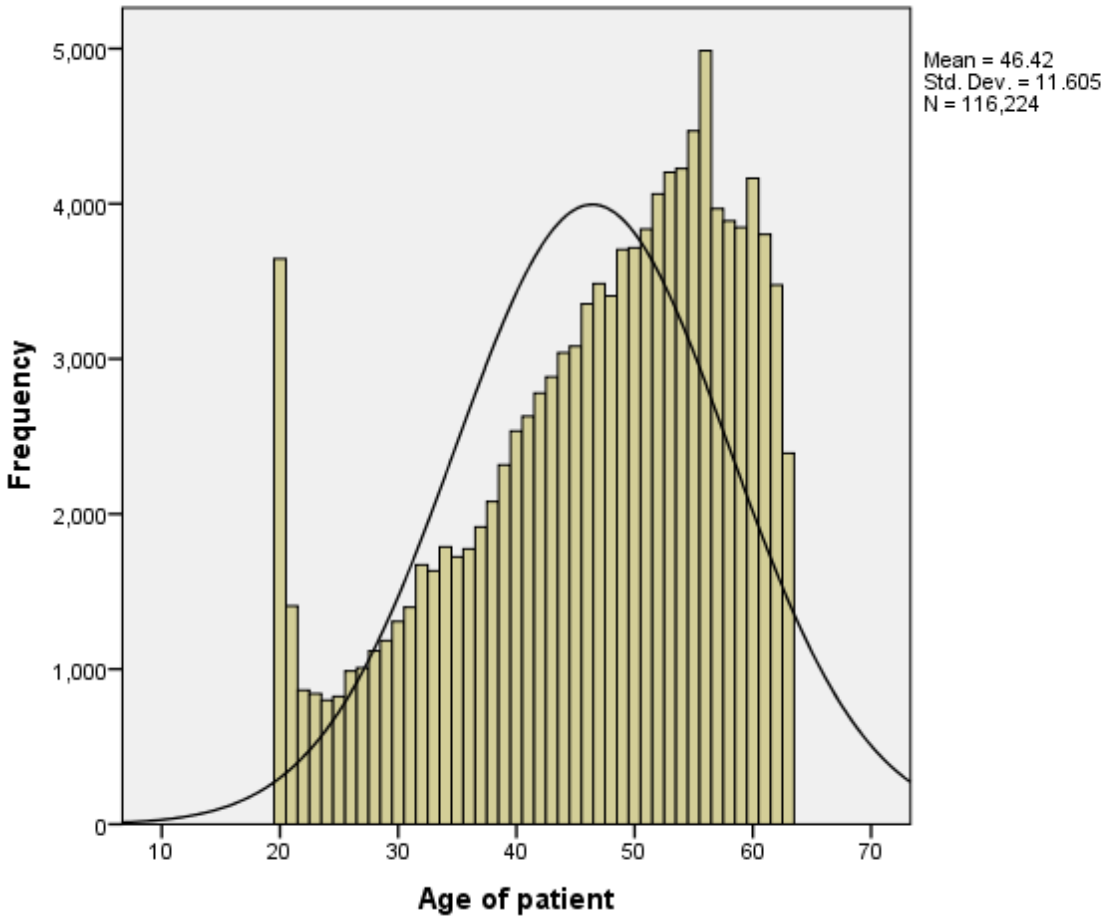


Figure A.2: Histogram (with normality plot) for Charlson comorbidity index score

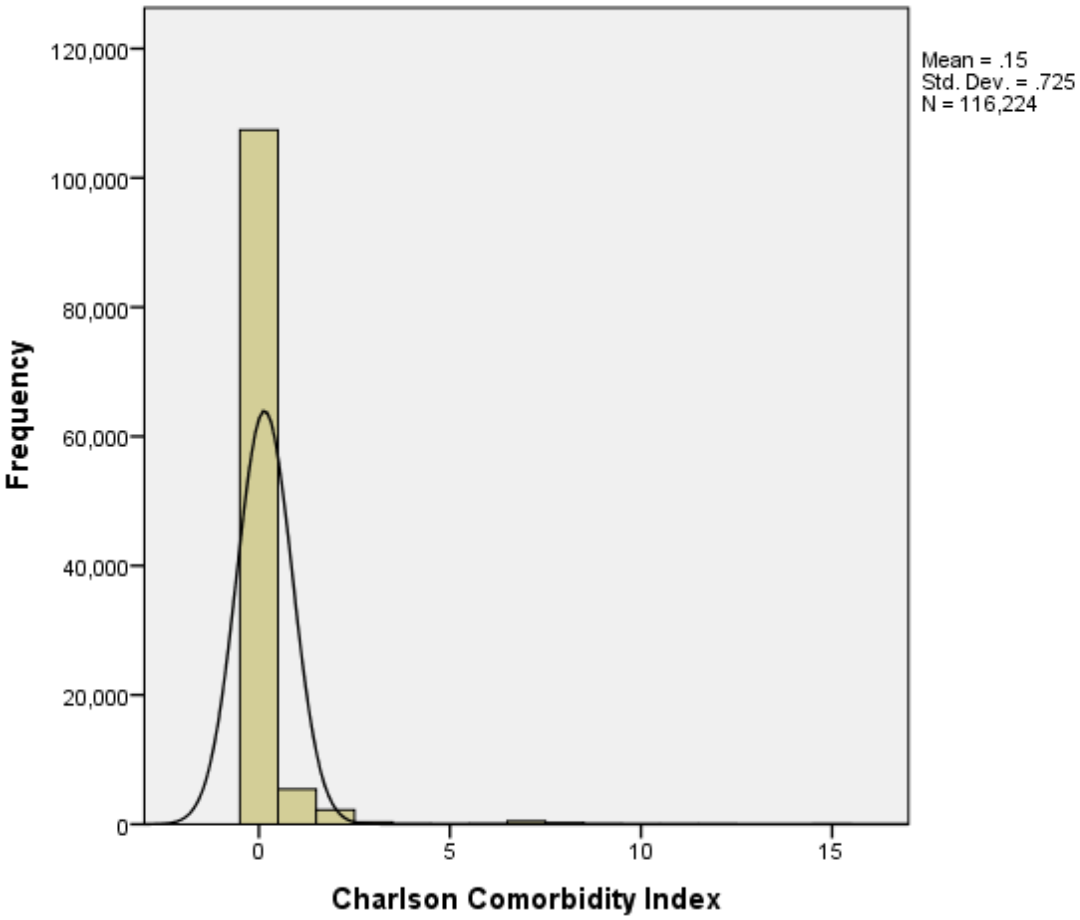


Figure A.3: Histogram (with normality plot) for medication possession ratio

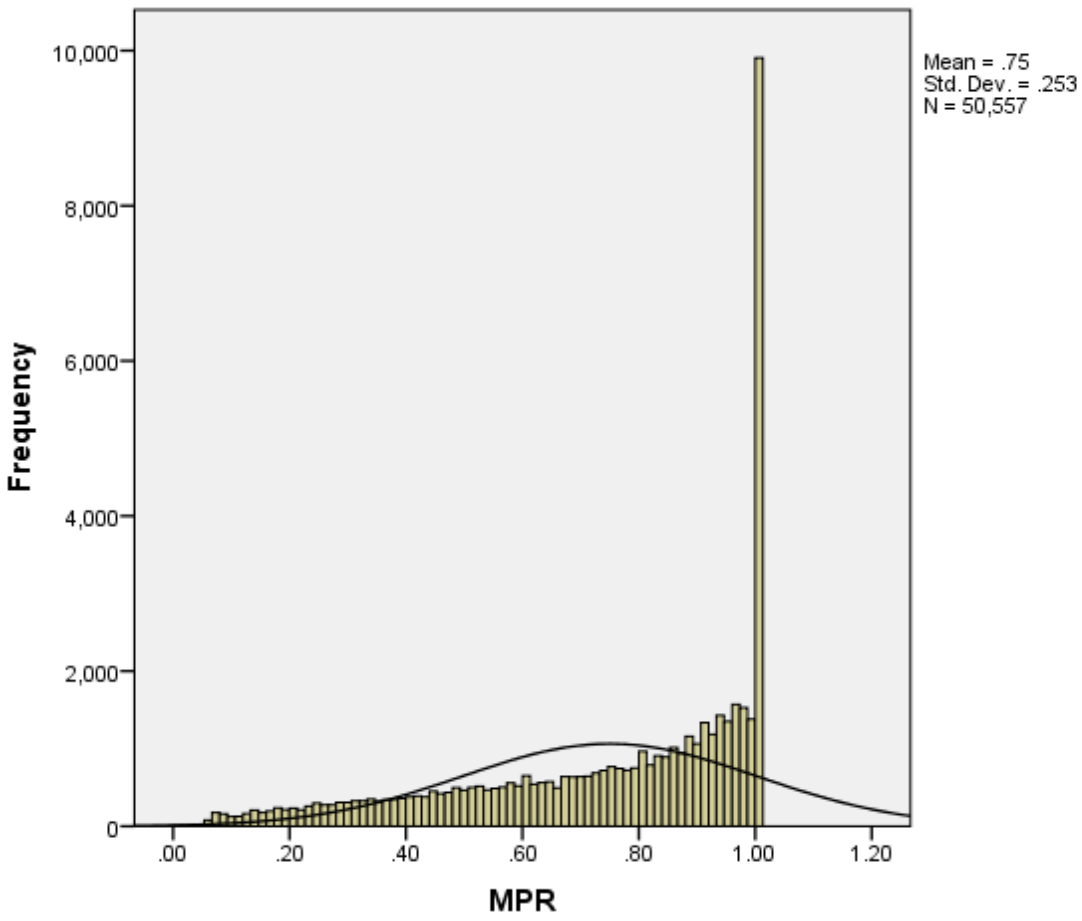


Figure A.4: Histogram (with normality plot) for 'number of prescriptions for all diabetogenic medications'

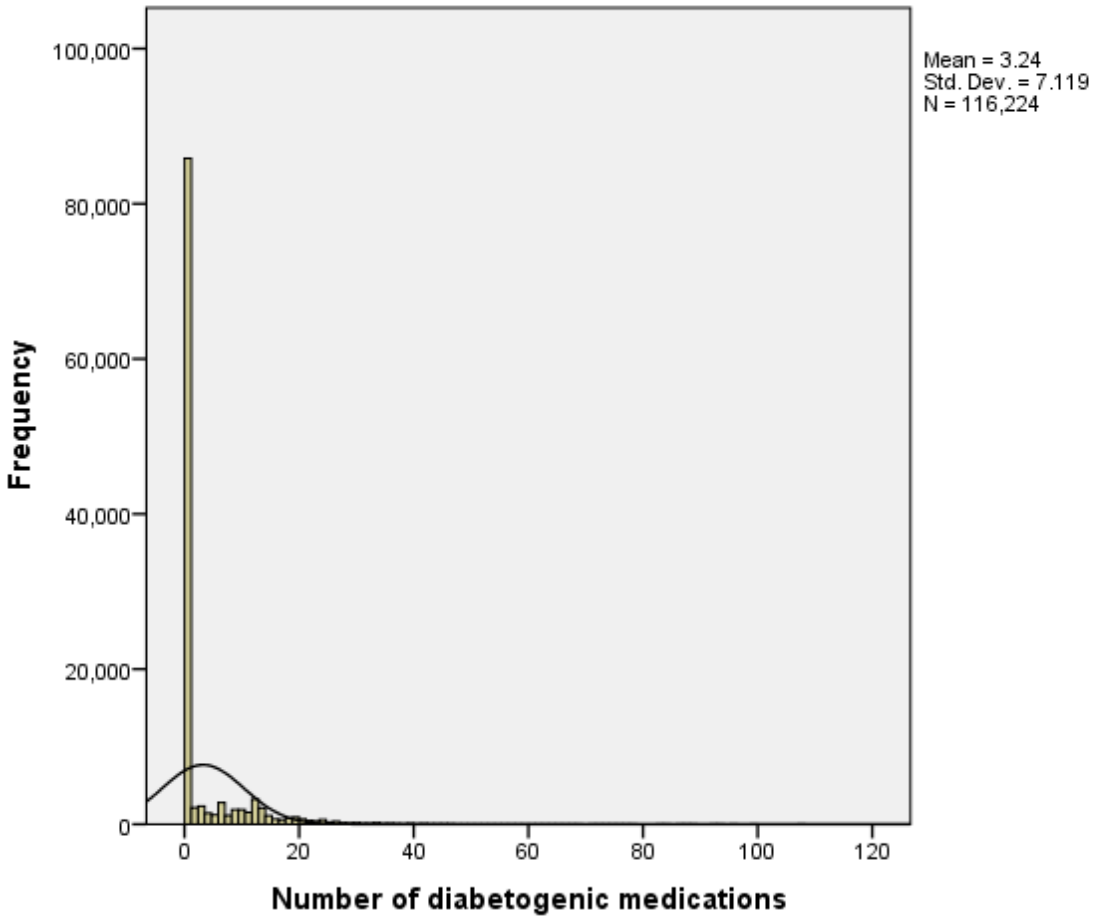


Figure A.5: Histogram (with normality plot) for number of prescriptions for thiazide diuretics

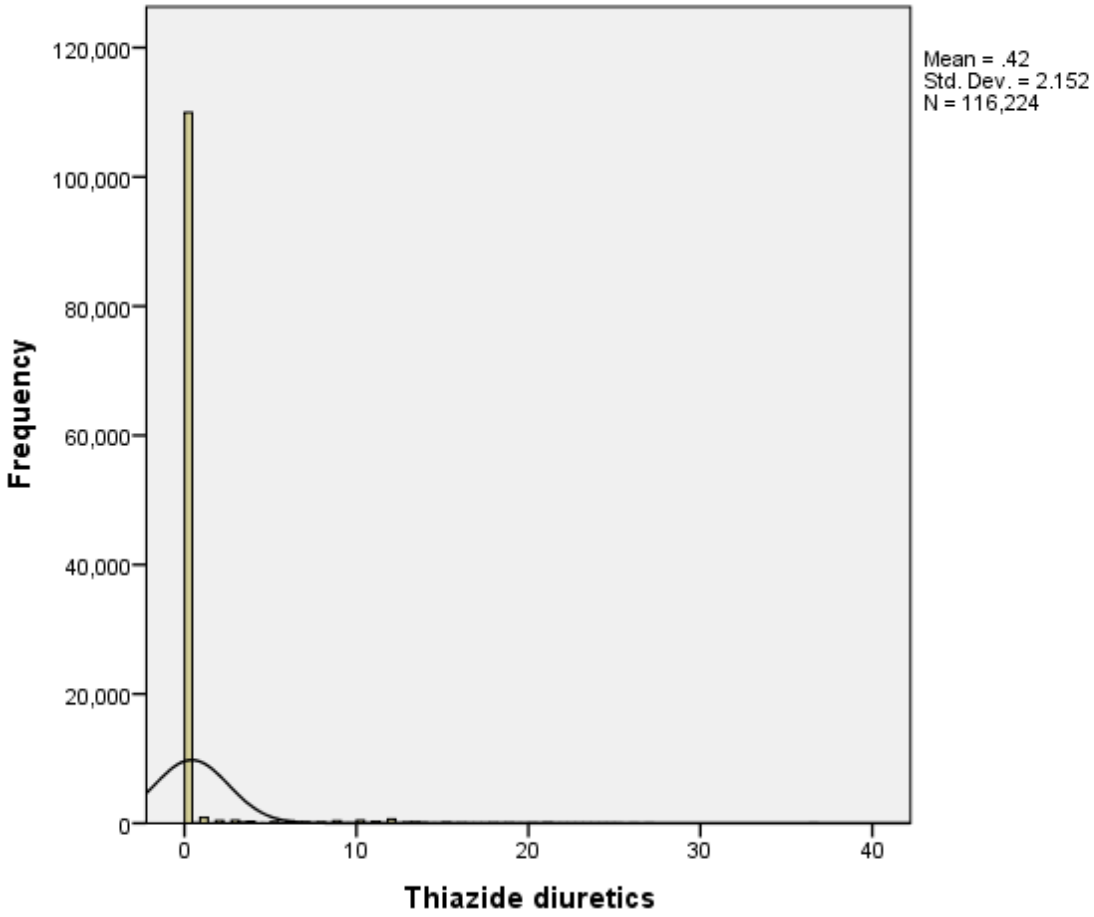


Figure A.6: Histogram (with normality plot) for number of prescriptions for beta-blockers

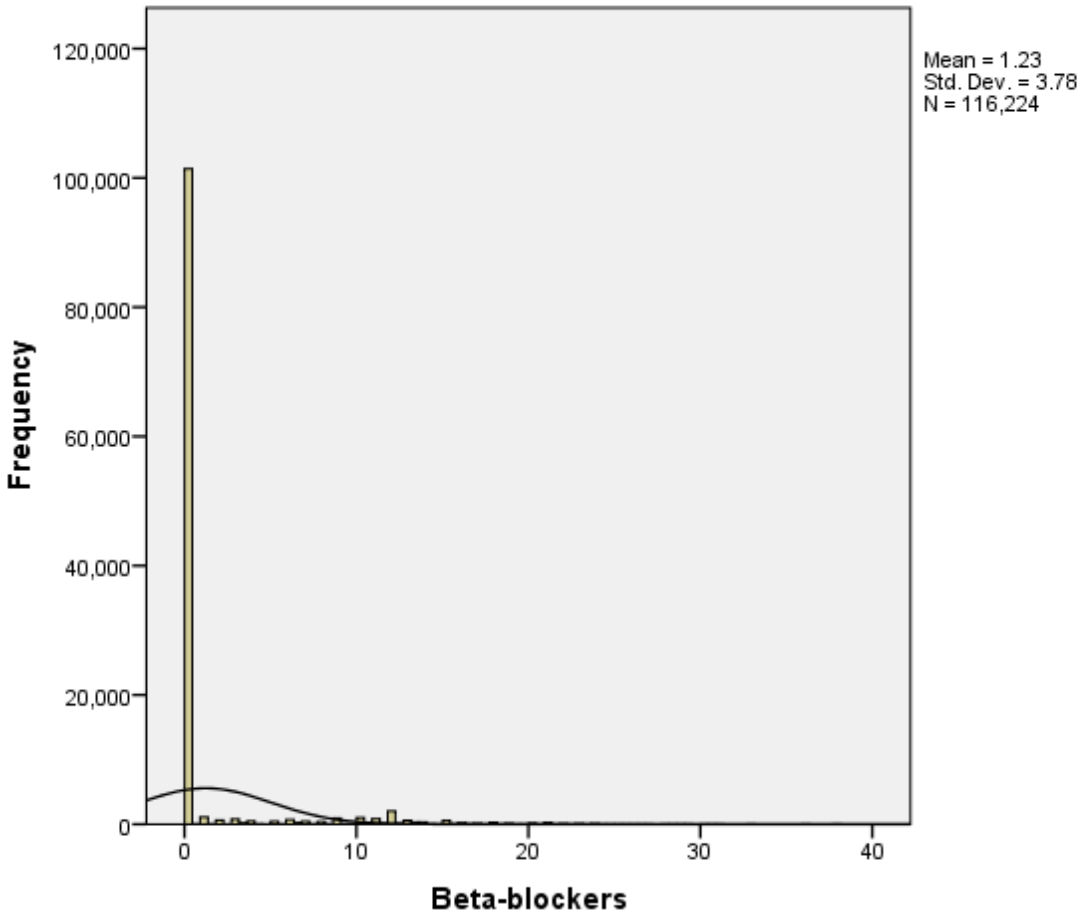


Figure A.7: Histogram (with normality plot) for number of prescriptions for antipsychotics

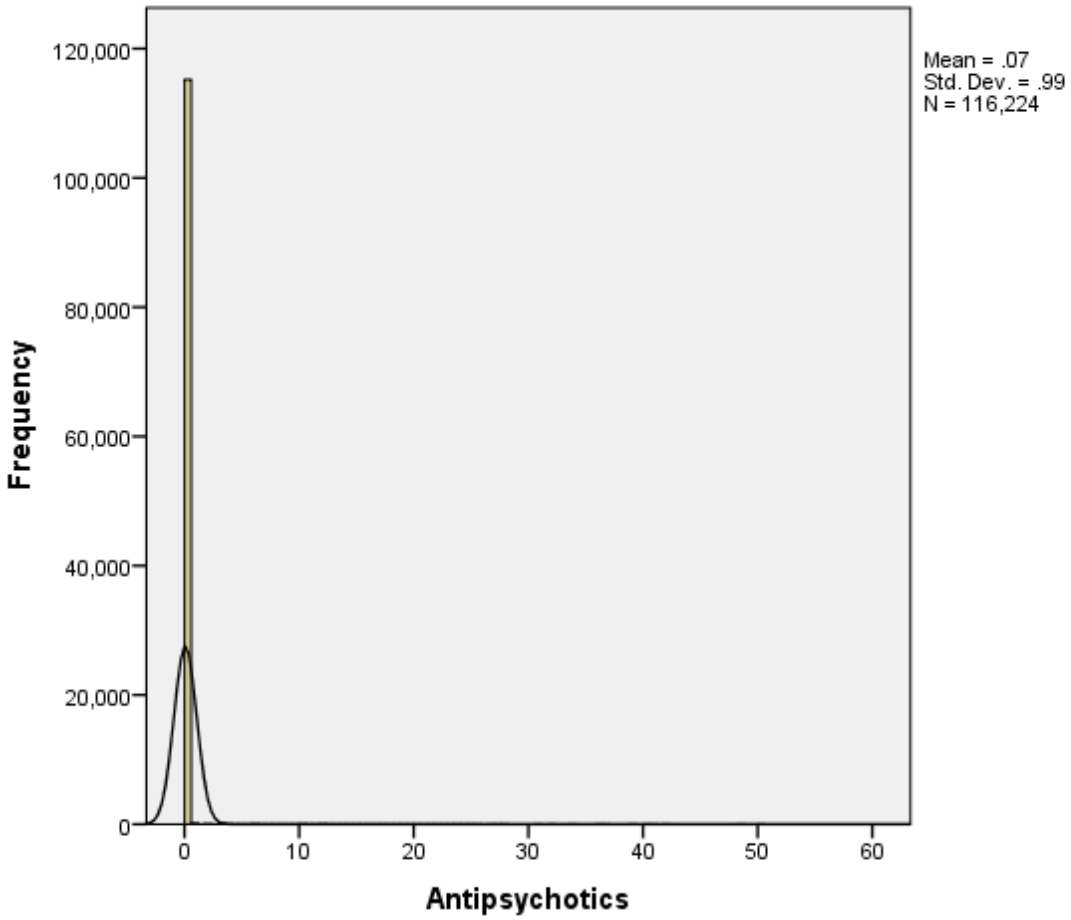


Figure A.8: Histogram (with normality plot) for number of prescriptions for antidepressants

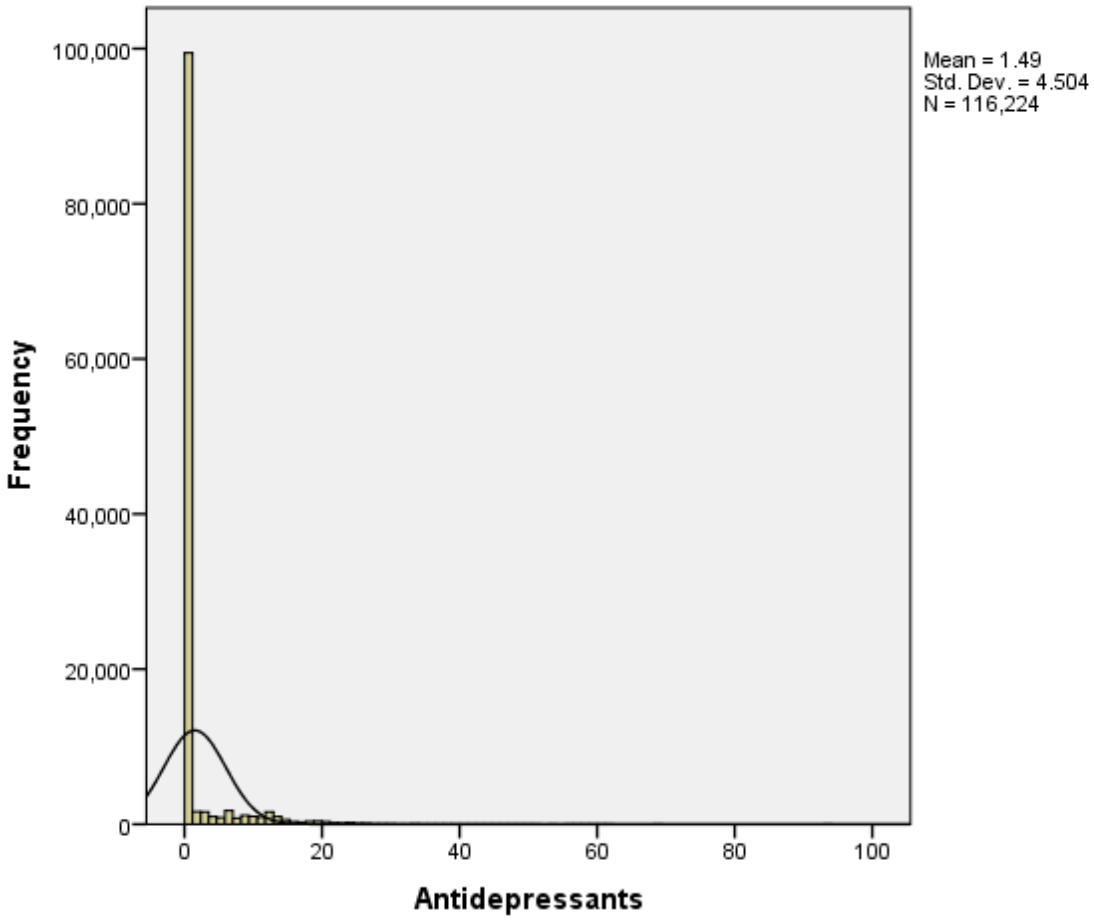


Figure A.9: Histogram (with normality plot) for number of prescriptions for immunosuppressants

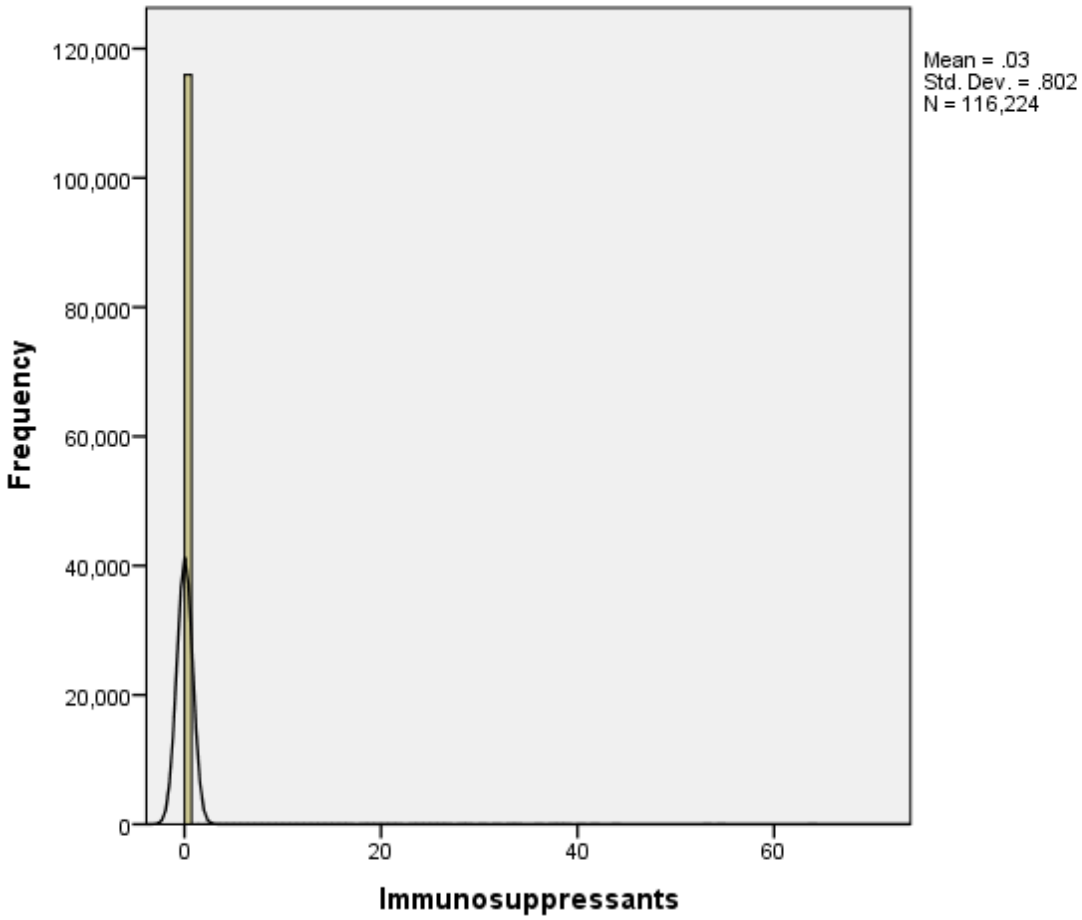
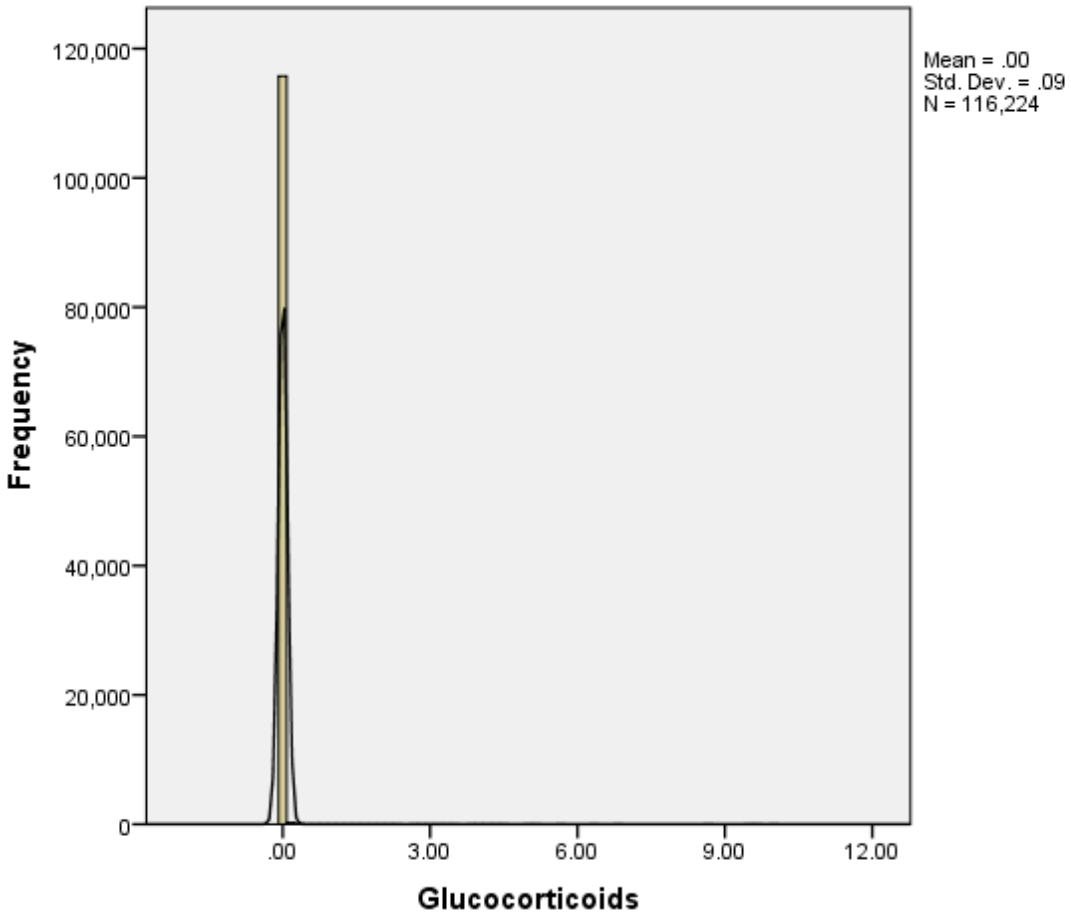


Figure A.10: Histogram (with normality plot) for number of prescriptions for glucocorticoids



APPENDIX B

SPSS Syntax for Cox Regression Model with Multiple Time-dependent Covariates

The following SPSS syntax shows how a Cox regression model with multiple time-dependent covariates can be run in SPSS. For the syntax below, gender, hyperlipidemia, hypertension, and diabetogenic variables were retained as significant time-dependent covariates (T_COV) that were controlled for in the model. Time-dependent covariates were formed by the product of the variable and the natural log (LN) of survival time (T_).

```
TIME PROGRAM.
COMPUTE T_COV_GENDER = LN(T_) * GENDER.
COMPUTE T_COV_HYPERLIPIDEMIA = LN(T_) * HYPERLIPIDEMIA.
COMPUTE T_COV_HYPERTENSION = LN(T_) * HYPERTENSION.
COMPUTE T_COV_DIABETOGENIC = LN(T_) * DIABETOGENIC.
COXREG   SURVIVAL_MONTHS
 /STATUS=DIABETES(1)
  /METHOD=ENTER EXPOSURE AGE GENDER HYPERLIPIDEMIA OBESITY
                HYPERTENSION DIABETOGENIC CCI T_COV_GENDER
                T_COV_HYPERLIPIDEMIA T_COV_HYPERTENSION
                T_COV_DIABETOGENIC
  /PRINT=CI(99)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

APPENDIX C

Cox Regression Models while Controlling for Time-dependent Covariates

Tables C.1 – C.7 shows a summary of the sensitivity analyses of the hazard ratios (Cox regression) of the association between statin use and incidence of diabetes when time-dependent covariates were controlled for in the models. The magnitudes of the hazard ratios for the predictor variables of interest (i.e., statin users and each statin type) increased by an average of 0.04 points from the hazard ratios in models that did not control for time-dependent covariates.

Table C.1: Cox Regression Model Comparing Incident Diabetes between Statin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=116,224)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Statin[a]	1.034	0.032	1053.572	**p<0.0001**	**2.812**	**2.590**	**3.052**
Age	0.032	0.001	530.516	p<0.0001	1.033	1.029	1.036
Gender: Male[b]	-0.014	0.038	0.130	0.719	0.986	0.894	1.088
Hyperlipidemia	-0.631	0.045	197.181	p<0.0001	0.532	0.474	0.597
Obesity	0.587	0.101	33.492	p<0.0001	1.798	1.385	2.334
Hypertension	0.436	0.043	101.132	p<0.0001	1.546	1.383	1.729
Diabetogenic medications	-0.221	0.008	679.054	p<0.0001	0.802	0.785	0.820
CCI score	0.134	0.009	213.121	p<0.0001	1.144	1.117	1.171
T_COV_Gender	-0.036	0.020	3.374	0.066	0.964	0.917	1.015
T_COV_Hyperlipidemia	0.127	0.023	31.733	p<0.0001	1.135	1.071	1.203
T_COV_Hypertension	-0.051	0.022	5.420	0.020	0.950	0.898	1.005
T_COV_Diabetogenic medications	0.085	0.004	555.755	p<0.0001	1.089	1.079	1.099

Model Parameters: χ^2=4,400.8; df=12, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

Table C.2: Cox Regression Model Comparing Incident Diabetes between Atorvastatin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=87,586)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Atorvastatin[a]	0.906	0.038	574.037	**p<0.0001**	**2.474**	**2.244**	**2.727**
Age	0.033	0.002	407.219	p<0.0001	1.034	1.030	1.038
Gender: Male[b]	0.053	0.049	1.147	0.284	1.054	0.929	1.196
Hyperlipidemia	-0.550	0.061	80.820	p<0.0001	0.577	0.493	0.676
Obesity	0.382	0.157	5.901	0.015	1.465	0.977	2.196
Hypertension	0.423	0.037	130.978	p<0.0001	1.526	1.388	1.679
Diabetogenic medications	-0.200	0.011	310.358	p<0.0001	0.819	0.795	0.843
CCI score	0.156	0.012	164.067	p<0.0001	1.168	1.132	1.205
T_COV_Gender	-0.077	0.025	9.288	0.002	0.926	0.868	0.988
T_COV_Hyperlipidemia	0.098	0.030	10.726	0.001	1.103	1.021	1.191
T_COV_Diabetogenic medications	0.076	0.005	253.610	p<0.0001	1.079	1.066	1.092

Model Parameters: χ^2=2,848.3; df=11, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable]..

Table C.3: Cox Regression Model Comparing Incident Diabetes between Fluvastatin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=59,911)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Fluvastatin[a]	0.729	0.088	68.786	**p<0.0001**	**2.072**	**1.653**	**2.599**
Age	0.048	0.004	181.267	p<0.0001	1.049	1.040	1.059
Gender: Male[b]	-0.049	0.044	1.228	0.268	0.953	0.851	1.066
Hyperlipidemia	-0.040	0.073	0.306	0.580	0.960	0.796	1.159
Obesity	0.204	0.334	0.372	0.542	1.226	0.518	2.901
Hypertension	0.674	0.072	88.675	p<0.0001	1.961	1.631	2.358
Diabetogenic medications	-0.276	0.032	73.634	p<0.0001	0.759	0.698	0.824
CCI score	0.174	0.027	41.524	p<0.0001	1.190	1.110	1.275
T_COV_Age	-0.007	0.002	16.703	p<0.0001	0.993	0.988	0.997
T_COV_Diabetogenic medications	0.115	0.013	75.964	p<0.0001	1.122	1.085	1.161

Model Parameters: χ^2=935.3; df=10, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

Table C.4: Cox Regression Model Comparing Incident Diabetes between Lovastatin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=62,166)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Lovastatin[a]	1.253	0.057	488.482	**p<0.0001**	**3.501**	**3.025**	**4.051**
Age	0.037	0.002	347.728	p<0.0001	1.038	1.033	1.043
Gender: Male[b]	0.072	0.068	1.141	0.285	1.075	0.903	1.280
Hyperlipidemia	-0.183	0.064	8.161	0.004	0.832	0.706	0.982
Obesity	0.484	0.185	6.810	0.009	1.622	1.006	2.614
Hypertension	0.624	0.062	100.579	p<0.0001	1.866	1.590	2.191
Diabetogenic medications	-0.356	0.029	146.911	p<0.0001	0.700	0.649	0.755
CCI score	0.159	0.024	44.075	p<0.0001	1.172	1.102	1.247
T_COV_Gender	-0.084	0.035	5.802	0.016	0.920	0.841	1.006
T_COV_Diabetogenic medications	0.138	0.012	134.904	p<0.0001	1.148	1.113	1.184

Model Parameters: χ^2=2,025.0; df=10, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

Table C.5: Cox Regression Model Comparing Incident Diabetes between Pravastatin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=64,495)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Pravastatin[a]	0.644	0.060	116.424	**p<0.0001**	**1.905**	**1.633**	**2.222**
Age	0.038	0.002	352.448	p<0.0001	1.038	1.033	1.044
Gender: Male[b]	0.063	0.068	0.863	0.353	1.065	0.894	1.268
Hyperlipidemia	-0.291	0.104	7.871	0.005	0.748	0.573	0.976
Obesity	0.187	0.290	0.416	0.519	1.205	0.572	2.541
Hypertension	0.641	0.059	116.940	p<0.0001	1.898	1.629	2.211
Diabetogenic medications	-0.187	0.020	89.068	p<0.0001	0.829	0.788	0.873
CCI score	0.173	0.020	76.227	p<0.0001	1.188	1.129	1.250
T_COV_Gender	-0.081	0.035	5.487	0.019	0.922	0.844	1.008
T_COV_Hyperlipidemia	0.091	0.050	3.359	0.067	1.096	0.964	1.246
T_COV_Diabetogenic medications	0.071	0.008	69.818	p<0.0001	1.074	1.050	1.097

Model Parameters: χ^2=1,414.8; df=11, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

Table C.6: Cox Regression Model Comparing Incident Diabetes between Rosuvastatin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=61,099)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Rosuvastatin[a]	0.510	0.082	38.601	**p<0.0001**	**1.665**	**1.348**	**2.057**
Age	0.036	0.002	303.968	p<0.0001	1.037	1.031	1.042
Gender: Male[b]	0.065	0.072	0.802	0.371	1.067	0.886	1.285
Hyperlipidemia	-0.007	0.070	0.009	0.923	0.993	0.829	1.190
Obesity	0.574	0.278	4.246	0.039	1.775	0.866	3.637
Hypertension	0.742	0.068	119.768	p<0.0001	2.100	1.764	2.501
Diabetogenic medications	-0.270	0.030	80.947	p<0.0001	0.763	0.706	0.824
CCI score	0.194	0.024	66.619	p<0.0001	1.214	1.142	1.291
T_COV_Gender	-0.084	0.037	5.221	0.022	0.919	0.836	1.011
T_COV_Diabetogenic medications	0.115	0.013	84.371	p<0.0001	1.122	1.086	1.159

Model Parameters: χ^2=1,014.4; df=10, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

Table C.7: Cox Regression Model Comparing Incident Diabetes between Simvastatin Users and Non-statin Users while Controlling for Covariates, including Time-dependent Covariates (N=71,527)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Simvastatin[a]	0.964	0.045	453.534	p<0.0001	2.622	2.334	2.946
Age	0.037	0.002	396.265	p<0.0001	1.037	1.032	1.042
Gender: Male[b]	-0.014	0.035	0.159	0.690	0.986	0.901	1.079
Hyperlipidemia	-0.394	0.077	25.919	p<0.0001	0.675	0.553	0.823
Obesity	0.659	0.187	12.442	p<0.0001	1.933	1.195	3.128
Hypertension	0.490	0.047	109.166	p<0.0001	1.632	1.446	1.841
Diabetogenic medications	-0.218	0.015	200.538	p<0.0001	0.804	0.773	0.836
CCI score	0.130	0.015	73.001	p<0.0001	1.139	1.095	1.184
T_COV_Hyperlipidemia	0.058	0.038	2.364	0.124	1.060	0.962	1.168
T_COV_Diabetogenic medications	0.083	0.007	161.663	p<0.0001	1.086	1.068	1.105

Model Parameters: χ^2=2,419.9; df=10, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Female.
T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

Table C.8: Cox Regression Model Comparing Incident Diabetes between Intensive-dose Statin Users and Moderate-dose Statin Users while Controlling for Covariates, including Time-dependent Covariates (N=71,527)							
	Parameter Estimate	Standard Error	Wald Chi-Square	**p-value**	**Hazard Ratio**	**99% Confidence Interval**	
						Lower	**Upper**
Dosage intensity: Intensive-dose[a]	0.432	0.039	121.963	**p<0.0001**	**1.540**	**1.393**	**1.704**
Age	0.020	0.003	41.800	p<0.0001	1.021	1.012	1.029
Gender: Male[b]	-0.088	0.046	3.593	0.058	0.916	0.812	1.032
Hyperlipidemia	-0.825	0.051	264.720	p<0.0001	0.438	0.385	0.499
Obesity	0.603	0.113	28.557	p<0.0001	1.828	1.367	2.445
Hypertension	0.271	0.049	30.084	p<0.0001	1.311	1.154	1.489
Diabetogenic medications	-0.233	0.009	630.494	p<0.0001	0.792	0.773	0.811
CCI score	0.122	0.010	137.855	p<0.0001	1.130	1.100	1.161
Adherence (MPR)[c]	0.020	0.056	0.126	0.723	1.020	0.883	1.178
T_COV_Age	0.004	0.002	4.910	0.027	1.004	0.999	1.008
T_COV_Gender	-0.014	0.024	0.350	0.554	0.986	0.926	1.049
T_COV_Hyperlipidemia	0.206	0.026	61.225	p<0.0001	1.228	1.148	1.315
T_COV_Hypertension	0.017	0.026	0.465	0.495	1.018	0.953	1.087
T_COV_Diabetogenic medications	0.090	0.004	509.669	p<0.0001	1.094	1.083	1.105

Model Parameters: χ^2=1,564.6; df=14, p<0.0001 [Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Female.

[c]Adherence evaluated using the medication possession ratio, MPR.

T_COV_: Time-dependent covariate [obtained by multiplying the natural log of survival time and the corresponding variable].

APPENDIX D

Diabetes Incidence Density Rate and Cumulative Incidence

Table D.1 shows the weighted and unweighted incidence density rates and cumulative incidence of diabetes by statin use. From Table D.1, the unweighted incidence density rate for statin users (6.82 per 1,000 person-months) was higher compared to that for non-statin users (2.2 per 1,000 person-months). This means that if 1,000 statin users were followed for one month, 6.82 new cases of diabetes will be recorded compared to 2.2 new cases of diabetes that will be recorded if 1,000 non-statin users were followed for one month.

Table D.1: Weighted[a] and Unweighted Incidence Density Rate and Cumulative Incidence of Diabetes by Statin Use (pre-index period for excluding prevalent diabetes=6 months)					
	Number of subjects $[\boldsymbol{a}]$	Sum of follow-up months (person-months) $[\boldsymbol{b}]$	Number of new cases of diabetes $[\boldsymbol{c}]$	Incidence density rates per 1,000 person-months $\left[{}^{\boldsymbol{c}}/_{\boldsymbol{b}} \times \mathbf{1000}\right]$	Cumulative incidence (in percent) $[{}^{\boldsymbol{c}}/_{\boldsymbol{a}} \times \mathbf{100}\%]$
Statin users	58,112	832,018.86	5,678	6.82	9.8
	2,682,918	38,396,263.29	268,287	6.99	10.0
Non-statin users	58,112	870,604.42	1,915	2.20	3.3
	2,296,349	34,429,716.96	80,006	2.32	3.5
Study population	116,224	1,702,623.28	7,593	4.45	6.5
	4,979,267	72,825,980.25	348,293	4.78	6.9
Atorvastatin users	29,474	424,669.37	2,690	6.33	9.1
	1,352,831	19,485,749.98	126,544	6.49	9.4
Fluvastatin users	1,799	25,991.59	192	7.39	10.7
	84,328	1,217,091.22	9,205	7.56	10.9
Lovastatin users	4,054	56,420.67	564	9.99	13.9
	203,368	2,826,918.77	29,049	10.28	14.3

[a]Weighted values are in shaded rows.

Table D.1: Weighted[a] and Unweighted Incidence Density Rate and Cumulative Incidence of Diabetes by Statin Use (cont'd)					
	Number of subjects $[\boldsymbol{a}]$	Sum of follow-up months (person-months) $[\boldsymbol{b}]$	Number of new cases of diabetes $[\boldsymbol{c}]$	Incidence density rates per 1,000 person-months $\left[{}^{\boldsymbol{c}}/_{\boldsymbol{b}} \times \mathbf{1000}\right]$	Cumulative incidence (in percent) $[{}^{\boldsymbol{c}}/_{\boldsymbol{a}} \times \mathbf{100}\%]$
Pravastatin users	6,383	93,339.04	587	6.29	9.2
	300,164	4,384,533.75	28,361	6.47	9.5
Rosuvastatin users	2,987	38,808.51	242	6.24	8.1
	134,386	1,744,581.78	11,266	6.46	8.4
Simvastatin users	13,415	192,789.68	1,403	7.42	10.5
	607,841	8,737,387.80	63,862	7.31	10.5
Intensive-dose statin users	6,205	87,639.06	831	9.48	13.4
	267,855	3,777,161.36	36,962	9.79	13.8
Moderate-dose statin users	51,907	744,379.79	4847	6.51	9.3
	2,415,063	34,619,101.93	231,325	6.68	9.6

[a]Weighted values are in shaded rows. *MarketScan* person-level national weights were constructed utilizing weight estimates from the Household Component of the Medical Expenditure Panel Survey (MEPS). MEPS's weights accounts for demographic variables that includes region (Northest, North Central, South, West); age (0 – 17, 18 – 44, 45 – 64); and sex (male, female). The *MarketScan* weight is the ratio of MEPS-based estimates in the different age/sex/region categories and the *MarketScan* number in the same category.

APPENDIX E

Unadjusted Cox Regression and Logistic Regression Models

Tables E.1 and E.2 shows a summary of the sensitivity analyses of the hazard ratios (Cox regression) and odds ratios (logistic regression) of the association between statin use and incident diabetes without controlling for any covariate. The covariates not controlled for include age, gender, hyperlipidemia, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR). In general, the values of the hazard and odds ratios associated with statin use increased significantly when none of the covariate was controlled for in the model. Risk ratios comparing intensive-dose users to moderate-dose users decreased.

Table E.1: A Summary Showing the Statistical Significance of the Unadjusted Hazard Ratios of the Association between Statin Use and Incident Diabetes (Cox Regression)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Hazard Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a]	1.128	0.026	1821.244	p<0.0001	**3.089**	2.886	3.307
Atorvastatin[a]	1.055	0.030	1244.233	p<0.0001	**2.871**	2.658	3.101
Fluvastatin[a]	1.210	0.076	255.585	p<0.0001	**3.354**	2.760	4.076
Lovastatin[a]	1.509	0.048	991.338	p<0.0001	**4.521**	3.996	5.115
Pravastatin[a]	1.050	0.047	495.666	p<0.0001	**2.859**	2.532	3.228
Rosuvastatin[a]	1.021	0.068	222.425	p<0.0001	**2.777**	2.328	3.313
Simvastatin[a]	1.194	0.035	1153.586	p<0.0001	**3.299**	3.014	3.612
Intensive-dose statin[b]	0.376	0.038	100.201	p<0.0001	**1.456**	1.322	1.604

Significance of each parameter estimate was evaluated at p<0.01. No covariate was controlled for in any of the model.
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.

Table E.2: A Summary Showing the Statistical Significance of the Unadjusted Odds Ratios of the Association between Statin Use and Incident Diabetes (Logistic Regression)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Odds Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a]	1.156	0.027	1818.301	p<0.0001	**3.178**	2.963	3.408
Atorvastatin[a]	1.081	0.031	1231	p<0.0001	**2.947**	2.722	3.191
Fluvastatin[a]	1.255	0.080	247.043	p<0.0001	**3.506**	2.855	4.306
Lovastatin[a]	1.557	0.051	932.010	p<0.0001	**4.742**	4.159	5.408
Pravastatin[a]	1.089	0.049	491.064	p<0.0001	**2.972**	2.619	3.373
Rosuvastatin[a]	0.951	0.071	179.398	p<0.0001	**2.587**	2.155	3.106
Simvastatin[a]	1.232	0.037	1135.827	p<0.0001	**3.428**	3.120	3.766
Intensive-dose statin[b]	0.406	0.040	102.122	p<0.0001	**1.501**	1.354	1.665

Significance of each parameter estimate was evaluated at p<0.01. No covariate was controlled for in any of the model.
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.

APPENDIX F

Cox Regression and Logistic Regression Models without Controlling for Obesity

Tables F.1 and F.2 shows a summary of the sensitivity analysis of the hazard and the odds ratios when the obesity variable was not controlled for in the Cox regression and logistic regression models of the association between statin use and incidence of diabetes. The obesity variable was left out because of the underreporting of obesity diagnosis (0.6%) among the study population. Removing the obesity variable from the model did not change the significance of the p-values. However, the magnitudes of the risk ratios increased only marginally.

Table F.1: A Summary Showing the Statistical Significance of the Hazard Ratios of the Association between Statin Use and Incident Diabetes (Cox regression without controlling for obesity)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Hazard Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	1.017	0.032	1020.014	p<0.0001	**2.765**	2.548	3.002
Atorvastatin[a,c]	0.888	0.038	551.155	p<0.0001	**2.430**	2.204	2.678
Fluvastatin[a,c]	0.726	0.088	68.723	p<0.0001	**2.067**	1.649	2.589
Lovastatin[a,c]	1.240	0.056	481.736	p<0.0001	**3.455**	2.988	3.997
Pravastatin[a,c]	0.637	0.060	114.121	p<0.0001	**1.890**	1.621	2.203
Rosuvastatin[a,c]	0.483	0.082	34.509	p<0.0001	**1.621**	1.311	2.003
Simvastatin[a,c]	0.945	0.045	436.293	p<0.0001	**2.574**	2.291	2.892
Intensive-dose statin[b,d]	0.423	0.039	116.595	p<0.0001	**1.526**	1.379	1.688

[Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Moderate-dose statin users.

[c]Covariates controlled for include age, gender, hyperlipidemia, hypertension, diabetogenic medications, and CCI score .

[d]Covariates controlled for include age, gender, hyperlipidemia, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

Table F.2: A Summary Showing the Statistical Significance of the Odds Ratios of the Association between Statin Use and Incident Diabetes (Logistic regression without controlling for obesity)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Odds Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	1.043	0.033	1004.646	p<0.0001	**2.838**	2.607	3.089
Atorvastatin[a,c]	0.912	0.039	542.014	p<0.0001	**2.490**	2.251	2.755
Fluvastatin[a,c]	0.772	0.092	69.818	p<0.0001	**2.164**	1.706	2.745
Lovastatin[a,c]	1.284	0.060	455.711	p<0.0001	**3.610**	3.092	4.215
Pravastatin[a,c]	0.669	0.062	116.047	p<0.0001	**1.953**	1.664	2.292
Rosuvastatin[a,c]	0.406	0.086	22.401	p<0.0001	**1.500**	1.203	1.871
Simvastatin[a,c]	0.978	0.047	428.901	p<0.0001	**2.658**	2.354	3.002
Intensive-dose statin[b,d]	0.456	0.043	114.588	p<0.0001	**1.578**	1.414	1.761

[Significance of each parameter estimate was evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Moderate-dose statin users.

[c]Covariates controlled for include age, gender, hyperlipidemia, hypertension, diabetogenic medications, and CCI score.

[d]Covariates controlled for include age, gender, hyperlipidemia, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

APPENDIX G

Pre-index Period Sensitivity Analysis

The purpose of this analysis was to investigate how changes to the length of the pre-index period affected the risk ratios associating statin use with incidence of diabetes. The length of the pre-index period that was used to identify and exclude prevalent diabetes cases in the original study design was 6 months. Sensitivity analyses were conducted by increasing the lengths of the pre-index period from 6 months to 1 year and then to 1.5 years. Diabetes incidence rates and risk ratios (i.e., hazard ratios and odds ratios) associating statin use with incidence of diabetes were then recalculated. The following results in Tables G.1 – G.12 were obtained.

Results and Discussion

1. Incidence of Diabetes

- 1,777 incident diabetes cases were reclassified as prevalent diabetes cases and removed from the study cohort when the pre-index period for identifying prevalent diabetes cases was increased from 6 months (Table G.1) to one year (Table G.2).
- 5,017 incident diabetes cases were reclassified as prevalent diabetes cases and removed from the study cohort when the pre-index period for identifying prevalent diabetes cases was increased from 6 months (Table G.1) to 1.5 years (Table G.3).

- The unadjusted cumulative incidence of diabetes and the unadjusted diabetes incidence density rates for the study population as well as for statin users and non-statin users decreased ‘significantly’ when the pre-index period was increased from 6 months (Table G.4) to 1 year (Table G.5) and then to 1.5 years (Table G.6).

Table G.1: Frequency and Percent of Statin Users and Non-statin Users by Incidence of Diabetes (6 months of pre-index period =Jan 1, 2003 – Jun 30, 2003)			
Diabetes	**Statin Users N (%)**	**Non-statin Users N (%)**	**Study Population N (%)**
Yes	5,678 (9.8)	1,915 (3.3)	7,593 (6.5)
No	52,434 (90.2)	56,197 (96.7)	108,631 (93.5)
Total	58,112 (100.0)	58,112 (100.0)	116,224 (100.0)
χ^2 = 1,995.2; df=1; p<0.0001			

Table G.2: Frequency and Percent of Statin Users and Non-statin Users by Incident Diabetes (1 year of pre-index period =Jan 1, 2003 – Dec 31, 2003)			
Diabetes	**Statin Users N (%)**	**Non-statin Users N (%)**	**Study Population N (%)**
Yes	4,315 (7.6)	1,501 (2.6)	5,816 (5.1)
No	52,434 (92.4)	56,197 (97.4)	108,631 (94.9)
Total	56,749 (100.0)	57,698 (100.0)	114,447 (100.0)
χ^2 = 1,484.1; df=1; p<0.0001			

Table G.3: Frequency and Percent of Statin Users and Non-statin Users by Incident Diabetes (1.5 years of pre-index period =Jan 1, 2003 – Jun 30, 2004)			
Diabetes	**Statin Users N (%)**	**Non-statin Users N (%)**	**Study Population N (%)**
Yes	1,878 (3.5)	698 (1.2)	2,576 (2.3)
No	52,434 (96.5)	56,197 (98.8)	108,631 (97.7)
Total	54,312 (100.0)	56,895 (100.0)	111,207 (100.0)
χ^2 = 611.2; df=1; p<0.0001			

Table G.4: Weighted[a] and Unweighted Incidence Density Rate and Cumulative Incidence of Diabetes by Statin Use (pre-index period for excluding prevalent diabetes=6 months)					
	Number of subjects [$\boldsymbol{a}$]	Sum of follow-up months (person-months) [$\boldsymbol{b}$]	Number of new cases of diabetes [$\boldsymbol{c}$]	Incidence density rates per 1,000 person-months $\left[{}^{\boldsymbol{c}}/_{\boldsymbol{b}} \times \mathbf{1000}\right]$	Cumulative incidence (in percent) $[{}^{\boldsymbol{c}}/_{\boldsymbol{a}} \times \mathbf{100}\%]$
Statin users	58,112	832,018.86	5,678	6.82	9.8
	2,682,918	38,396,263.29	268,287	6.99	10.0
Non-statin users	58,112	870,604.42	1,915	2.20	3.3
	2,296,349	34,429,716.96	80,006	2.32	3.5
Study population	116,224	1,702,623.28	7,593	4.45	6.5
	4,979,267	72,825,980.25	348,293	4.78	6.9

[a]Weighted values are in shaded rows. *MarketScan* person-level national weights were constructed utilizing weight estimates from the Household Component of the Medical Expenditure Panel Survey (MEPS). MEPS's weights accounts for demographic variables that includes region (Northest, North Central, South, West); age (0 – 17, 18 – 44, 45 – 64); and sex (male, female). The *MarketScan* weight is the ratio of MEPS-based estimates in the different age/sex/region categories and the *MarketScan* number in the same category.

Table G.5: Weighted[a] and Unweighted Incidence Density Rate and Cumulative Incidence of Diabetes by Statin Use (pre-index period for excluding prevalent diabetes=1 year)					
	Number of subjects $[\boldsymbol{a}]$	Sum of follow-up months (person-months) $[\boldsymbol{b}]$	Number of new cases of diabetes $[\boldsymbol{c}]$	Incidence density rates per 1,000 person-months $\left[{}^{\boldsymbol{c}}/_{\boldsymbol{b}} \times \mathbf{1000}\right]$	Cumulative incidence (in percent) $[{}^{\boldsymbol{c}}/_{\boldsymbol{a}} \times \mathbf{100}\%]$
Statin users	56,749	829,714.83	4,315	5.20	7.6
	2,619,961	38,289,211.37	205,330	5.36	7.8
Non-statin users	57,698	869,975.34	1,501	1.73	2.6
	2,279,498	34,403,944.31	63,155	1.84	2.8
Study population	114,447	1,699,690.17	5,816	3.42	5.1
	4,899,459	72,693,155.68	268,485	3.69	5.5
Table G.6: Weighted[a] and Unweighted Incidence Density Rate and Cumulative Incidence of Diabetes by Statin Use (pre-index period for excluding prevalent diabetes=1.5 years)					
Statin users	54,312	815,384.15	1,878	2.30	3.5
	2,504,997	37,609,199.80	90,366	2.40	3.6
Non-statin users	56,895	865,118.46	698	0.81	1.2
	2,246,090	34,201,951.93	29,747	0.87	1.3
Study population	111,207	1,680,502.60	2,576	1.53	2.3
	4,751,087	71,811,151.74	120,113	1.67	2.5

[a]Weighted values are in shaded rows.

2. Cox regression

- The hazard ratios for statin users and for users of each statin type reduced 'slightly' and remained statistically significant when the pre-index period for identifying prevalent diabetes cases was increased from 6 months (Table G.7) to 1 year (Table G.8).
- In contrast, the hazard ratios for statin users and for users of each statin type reduced 'substantially' when the pre-index period for identifying prevalent diabetes cases was increased from 6 months (Table G.7) to 1.5 years (Table G.9).
- In fact, the hazard ratio for pravastatin was no longer significant (p=0.048) when the pre-index period was 1.5 years (Table G.9).

Table G.7: Cox Regression (6 months of pre-index period for excluding prevalent diabetes cases, N=116,224)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Hazard Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	1.012	0.032	1009.438	p<0.0001	**2.752**	2.535	2.987
Atorvastatin[a,c]	0.886	0.038	548.135	p<0.0001	**2.425**	2.200	2.673
Fluvastatin[a,c]	0.725	0.088	68.452	p<0.0001	**2.064**	1.647	2.586
Lovastatin[a,c]	1.228	0.057	466.996	p<0.0001	**3.413**	2.949	3.951
Pravastatin[a,c]	0.636	0.060	113.865	p<0.0001	**1.889**	1.620	2.202
Rosuvastatin[a,c]	0.480	0.082	34.043	p<0.0001	**1.615**	1.307	1.996
Simvastatin[a,c]	0.943	0.045	433.518	p<0.0001	**2.567**	2.284	2.884
Intensive-dose statin[b,d]	0.422	0.039	116.165	p<0.0001	**1.525**	1.378	1.686

[Significance of each parameter estimate is evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.
[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.
[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

Table G.8: Cox Regression (1 year of pre-index period for excluding prevalent diabetes cases, N=114,447)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Hazard Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	0.913	0.037	625.225	p<0.0001	**2.491**	2.267	2.737
Atorvastatin[a,c]	0.797	0.044	334.815	p<0.0001	**2.218**	1.983	2.481
Fluvastatin[a,c]	0.719	0.099	52.261	p<0.0001	**2.053**	1.589	2.652
Lovastatin[a,c]	1.059	0.068	244.622	p<0.0001	**2.883**	2.422	3.433
Pravastatin[a,c]	0.563	0.069	66.859	p<0.0001	**1.756**	1.471	2.097
Rosuvastatin[a,c]	0.616	0.090	46.532	p<0.0001	**1.851**	1.467	2.336
Simvastatin[a,c]	0.858	0.052	270.338	p<0.0001	**2.358**	2.062	2.697
Intensive-dose statin[b,d]	0.399	0.045	77.624	p<0.0001	**1.490**	1.326	1.674

[Significance of each parameter estimate is evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.
[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.
[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

Table G.9: Cox Regression (1.5 years of pre-index period for excluding prevalent diabetes cases, N=111,207)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Hazard Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	0.688	0.055	157.815	p<0.0001	**1.989**	1.727	2.290
Atorvastatin[a,c]	0.624	0.065	93.344	p<0.0001	**1.866**	1.580	2.203
Fluvastatin[a,c]	0.420	0.152	7.677	0.006	**1.523**	1.030	2.251
Lovastatin[a,c]	0.685	0.107	41.308	p<0.0001	**1.984**	1.507	2.610
Pravastatin[a,c]	0.210	0.106	3.910	**0.048**	**1.234**	0.938	1.623
Rosuvastatin[a,c]	0.414	0.139	8.914	0.003	**1.513**	1.058	2.161
Simvastatin[a,c]	0.533	0.081	43.616	p<0.0001	**1.705**	1.385	2.099
Intensive-dose statin[b,d]	0.295	0.070	17.596	p<0.0001	**1.343**	1.121	1.611

[Significance of each parameter estimate is evaluated at p<0.01].

[a]Reference=Non-statin users.

[b]Reference=Moderate-dose statin.

[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.

[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

3. Logistic regression

- Similar to the Cox regression analysis results, the odds ratios for statin users and for users of each statin type reduced 'slightly' and remained statistically significant when the pre-index period for identifying prevalent diabetes cases was increased from 6 months (Table G.10) to 1 year (Table G.11).
- In contrast, the odds ratios for statin users and for users of each statin type reduced 'substantially' when the pre-index period for identifying prevalent diabetes cases was increased from 6 months (Table G.10) to 1.5 years (Table G.12).
- In fact, the hazard ratios for pravastatin (p=0.026) and rosuvastatin (p=0.325) were no longer significant when the pre-index period was 1.5 years (Table G.12).

Table G.10: Logistic Regression (6 months of pre-index period for excluding prevalent diabetes cases, N=116,224)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Odds Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	1.038	0.033	993.897	p<0.0001	**2.824**	2.594	3.074
Atorvastatin[a,c]	0.910	0.039	538.842	p<0.0001	**2.485**	2.246	2.749
Fluvastatin[a,c]	0.771	0.092	69.572	p<0.0001	**2.161**	1.704	2.742
Lovastatin[a,c]	1.271	0.060	442.002	p<0.0001	**3.565**	3.051	4.165
Pravastatin[a,c]	0.669	0.062	115.773	p<0.0001	**1.952**	1.663	2.290
Rosuvastatin[a,c]	0.402	0.086	22.000	p<0.0001	**1.495**	1.199	1.865
Simvastatin[a,c]	0.975	0.047	426.171	p<0.0001	**2.651**	2.347	2.994
Intensive-dose statin[b,d]	0.456	0.043	114.477	p<0.0001	**1.578**	1.414	1.761

[Significance of each parameter estimate is evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.
[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.
[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

Table G.11: Logistic Regression (1 year of pre-index period for excluding prevalent diabetes cases, N=114,447)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Odds Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	0.929	0.037	615.966	p<0.0001	**2.533**	2.300	2.789
Atorvastatin[a,c]	0.813	0.045	330.226	p<0.0001	**2.255**	2.009	2.530
Fluvastatin[a,c]	0.754	0.104	52.813	p<0.0001	**2.125**	1.627	2.775
Lovastatin[a,c]	1.080	0.071	233.524	p<0.0001	**2.946**	2.456	3.535
Pravastatin[a,c]	0.589	0.071	68.745	p<0.0001	**1.803**	1.501	2.165
Rosuvastatin[a,c]	0.505	0.093	29.280	p<0.0001	**1.657**	1.303	2.107
Simvastatin[a,c]	0.882	0.054	268.002	p<0.0001	**2.416**	2.103	2.776
Intensive-dose statin[b,d]	0.426	0.048	78.384	p<0.0001	**1.532**	1.353	1.734

[Significance of each parameter estimate is evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.
[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.
[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

Table G.12: Logistic Regression (1.5 years of pre-index period for excluding prevalent diabetes cases, N=111,207)							
	Parameter Estimate	Standard Error	Wald Chi-Square	p-value	**Odds Ratio**	99% Confidence Interval	
						Lower	Upper
Statin[a,c]	0.686	0.055	153.580	p<0.0001	**1.987**	1.722	2.291
Atorvastatin[a,c]	0.626	0.065	91.656	p<0.0001	**1.871**	1.581	2.214
Fluvastatin[a,c]	0.446	0.155	8.328	0.004	**1.563**	1.049	2.328
Lovastatin[a,c]	0.673	0.108	38.581	p<0.0001	**1.960**	1.483	2.591
Pravastatin[a,c]	0.241	0.108	4.984	0.026	**1.272**	.964	1.680
Rosuvastatin[a,c]	0.138	0.140	0.969	0.325	**1.148**	.800	1.647
Simvastatin[a,c]	0.547	0.082	44.567	p<0.0001	**1.728**	1.399	2.133
Intensive-dose statin[b,d]	0.320	0.072	19.631	p<0.0001	**1.377**	1.143	1.658

[Significance of each parameter estimate is evaluated at p<0.01].
[a]Reference=Non-statin users.
[b]Reference=Moderate-dose statin.
[c]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, and CCI score.
[d]Covariates controlled for include age, gender, hyperlipidemia, obesity, hypertension, diabetogenic medications, CCI score, and medication possession ratio (MPR).

Conclusion

The length of the pre-index period used to identify and exclude prevalent diabetes cases matters (as hypothesized in the dissertation discussion section) when estimating the association between statin use and incidence of diabetes. A pre-index period of at least 1.5 – 2 years is more robust for establishing a history of diabetes.

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